

A THESIS  
presented for the degree  
of  
DOCTOR OF SCIENCE  
of  
THE UNIVERSITY OF EDINBURGH  
-----

By  
JOHN MASSON GULLAND  
B.Sc. Edinburgh, 1921.  
M.A. (Oxford), Ph.D. (St. Andrews),  
University Demonstrator in Chemistry  
in  
The University of Oxford.

.....



## DECLARATION.

A thesis submitted to the University of St. Andrews for the Doctorate of Philosophy contained the practical work which is described in Publications 3, 5, and 6, and included the theoretical ideas of Publications 1 and 2, but did not contain the modified views on the constitution of morphine which are recorded in Publication 3. The work which is described in the remaining publications, with the exception of one of the isolated experiments which have been recorded in the literature, has not been submitted for publication.

### T H E

### MORPHINE AND APORPHINE

### ALKALOIDS

## DECLARATION.

-----

A thesis submitted to the University of St. Andrews for the Doctorate of Philosophy contained the practical work which is described in Publications 2, 3, and 4, and embodied the theoretical ideas of Publications 1 and 2, but did not contain the modified views on the constitution of morphine which are recorded in Publication 3. The work which is described in the remaining publications, with the exception of one or two isolated experiments which have been repeated and extended since that date, has not been submitted for any Degree.

I feel that some explanation should be made of the reason why part of the experimental work on the aporphine alkaloids has been carried out in collaboration. One of the essential features of this work has been the necessity for speed, in order to compete with the work of other investigators who are in a position to avail themselves of more assistance than is at my disposal. This need for haste requires no illustration beyond the direction of attention to three facts. Firstly, the publication of the syntheses of bulbocapnine methylether and of corytuberine dimethylether forestalled by one month in each case the appearance of papers on these subjects by Späth and his collaborators. Secondly, the results obtained from the work on the constitution of laurotetanine have been anticipated by a

# PUBLICATIONS.

few days by the publications of Späth and of Barger and their co-workers. Finally, a paper entitled "The synthesis of apomorphine dimethylether" was read by Pschorr and his assistants at a meeting held in Berlin on December 8th (Ber. 1928, December).

It is clearly stated on each joint Publication what has been my share in the experimental work.

This thesis has been entirely composed by myself.

1. Styracine and brucine. Part 1.
2. The condensation of certain of the morphine group.
3. Synthetical experiments on the aporphine group. Part 1. December 1928.
4. The constitution of thebaine.
5. Synthetical experiments on the aporphine group. Part 2.
6. The isomeris 2-aminoacrylamino acids.
7. Synthetical experiments on the aporphine alkaloids. Part 3.
8. Synthetical experiments on the aporphine alkaloids. Part 4.
9. At the end of the thesis.
10. The condensation of 5-nitro-3:4-dimethoxybenzyl cyanide with picro-bases.
11. Nitro-derivatives of 3:4-dihydroxyphenylacetic acid.
12. Attempted synthesis of phenolic aporphines.
13. The constitution of isurotetanine.
14. The constitution of isobutaine.
15. Attempted synthesis of apomorphine dimethylether.



## PUBLICATIONS.

-----

### In separate volume.

1. The morphine group. Part 1.
2. The morphine group. Part 2.
3. The constitution of codeine and thebaine.
4. Synthetical experiments in the naphthyridine groups.
5. Derivatives of homocatechol. Part 1.
6. Derivatives of homocatechol. Part 2.
7. Strychnine and brucine. Part 5.
8. The condensation of certain aldehydes with ketones of the morphine group.
9. Synthetical experiments on the aporphine group. Part 1.
10. The constitution of thebenine.
11. Synthetical experiments on the aporphine group. Part 2.
12. The isomeric 2-aminoarylcinnamic acids.
13. Synthetical experiments on the aporphine alkaloids. Part 3.
14. Synthetical experiments on the aporphine alkaloids. Part 4.

### At the end of the thesis.

15. The condensation of 2-nitro-3:4-dimethoxybenzyl cyanide with pseudo-bases.
16. Nitro-derivatives of 3:4-dihydroxyphenylacetic acid.
17. Attempted synthesis of phenolic aporphines.
18. The constitution of laurotetanine.
19. The constitution of isothebaine.
20. Attempted synthesis of apomorphine dimethylether.

## CONTENTS.

-----

<u>The Morphine Alkaloids.</u>	Page
Introduction.	1.
The constitution of dihydrocodeine.	3.
The unsaturation of codeine.	25.
The salient features of morphine chemistry.	29.
The action of acids on thebaine.	40.
The reduction of thebaine.	70.
The deoxy-compounds and some stereochemical relationships.	76.
<u>The Aporphine Alkaloids.</u>	
Introduction	82.
The reactions of the aporphines.	85.
Classification of the aporphine bases.	90.
Synthetical experiments in connection with the aporphine alkaloids.	106.
<u>Addendum.</u>	
The constitution of sinomenine.	
<u>Unpublished papers.</u>	

PART I.

THE CONSTITUTION OF THE MORPHINE ALKALOIDS.

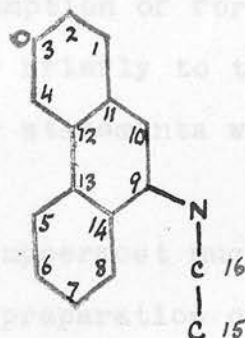
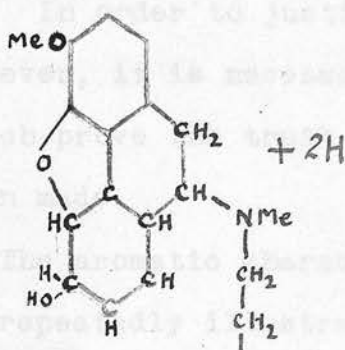
## INTRODUCTION.

---

In any general survey of the researches of the past fifty years in the wide field of alkaloidal chemistry, it is clear that no problem has exercised a greater fascination for chemists or has received more attention than that of the constitution of morphine. The complexity of the structures involved, the intricacy of the reactions which they undergo, and the obvious importance of these structures and reactions to medical science has attracted a very large number of workers. The great mass of evidence which has accumulated from their studies renders it an impossible task either to approach the subject from what would be the most natural starting point - namely the historical point of view, or even to mention each of the individual researches which have been devised to attack the problem. It will be necessary therefore to assume a formula, or rather a part-formula, to justify this by reference to some of the experiments which have a direct bearing on the points involved, and to pass from such a part-formula to the consideration of the questions which then remain unanswered.

The sensitivity of morphine to oxidation has caused most investigators to restrict themselves to the use of

codeine or thebaine, and accordingly most of the compounds which come under consideration contain the phenolic hydroxyl group of morphine in the form of its methyl ether, and are thus derivatives of codeine. The author therefore proposes (I) as a part-formula for dihydrocodeine, a base produced by the catalytic reduction of codeine, and wishes to attack the problem of the constitution of the alkaloids with this as a fundamental assumption. It will be noted that the valencies of three carbon atoms in ring III are unsatisfied and that one carbon linkage and two hydrogen atoms are available for this purpose.



### THE CONSTITUTION OF DIHYDROCODEINE

The researches of Freund, Knorr, Pschorr, Vongerichten, and their collaborators have fully demonstrated the following points in connection with the morphine alkaloids:-

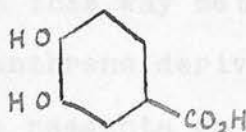
- A. The aromatic character of one nucleus:
- B. The existence of a phenanthrene skeleton with a tertiary methylamino-group attached to it directly and also through a chain of two carbon atoms not included in the nucleus:
- C. The position of the phenolic and alcoholic hydroxyl groups:
- D. The existence of an ether-oxygen bridge.

In order to justify the assumption of formula (I), however, it is necessary to refer briefly to the experiments which prove the truth of the four statements which have just been made.

- A. The aromatic character of the uppermost nucleus has been repeatedly illustrated by the preparation of the normal benzenoid derivatives, e.g. nitrocodeine, codeine sulphonic acid, bromomorphine, and several others. The substituent remains unaffected throughout the transformations for which the group of compounds is noted, and is either in position 1 or 2. Moreover, the ring contains a phenolic hydroxyl or its methyl ether, and remains unaffected by those reactions which attack the rest of the molecule.

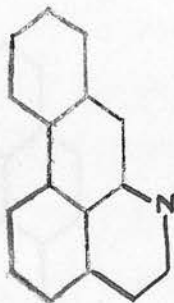


In connection with this nucleus, it is interesting to note the production by Barth and Weidel<sup>1</sup> of protocathevic acid (II) by the fusion of morphine with alkali.



II.

B. By distilling morphine with zinc dust, Vongerichten<sup>2</sup> and Schrötter obtained ammonia, trimethylamine, phenanthrene, pyridine, and two other bases. One of these was probably quinoline, and the other was shown to be morphidine, or phananthrene quinoline (III).



III.

This degradation to nitrogenous and nitrogen-free compounds of known constitution was evidently of the greatest importance in determining the morphine skeleton. Although it appeared highly probable that the fundamental basis of the structure was phenanthrene, the high temperature at

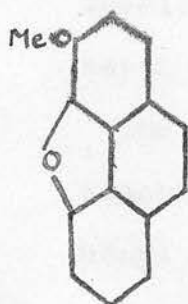
---

\* In order to maintain the continuity of the text, the numerous references are collected together at the end of the theoretical discussion.

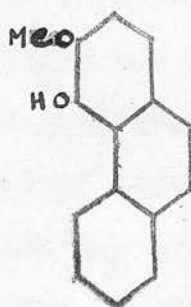


which the reaction had to be carried out might readily have caused secondary changes to take place. Vongerichten and Schrötter decided, therefore, to eliminate the nitrogen<sup>3</sup> atom by exhaustive methylation (Hofmann), and these authors<sup>4</sup> and Hesse obtained in this way methyl morphenol. (IV).

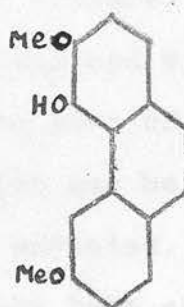
Many other true phenanthrene derivatives have been produced by the use of various reagents on thebaine or derivatives of the alkaloids, and examples of such compounds are methyl morphol (V) and its methyl ether, thebaol (VI), 3. methoxy 4.6. dioxo-phenanthrene (VII), and the trimethoxy-vinyl-phenanthrenes which have resulted from the exhaustive methylation of the methyl ethers of morphothebaine, apomorphine, and thebenine.



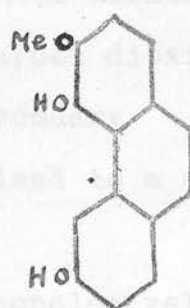
IV



V



VI



VII

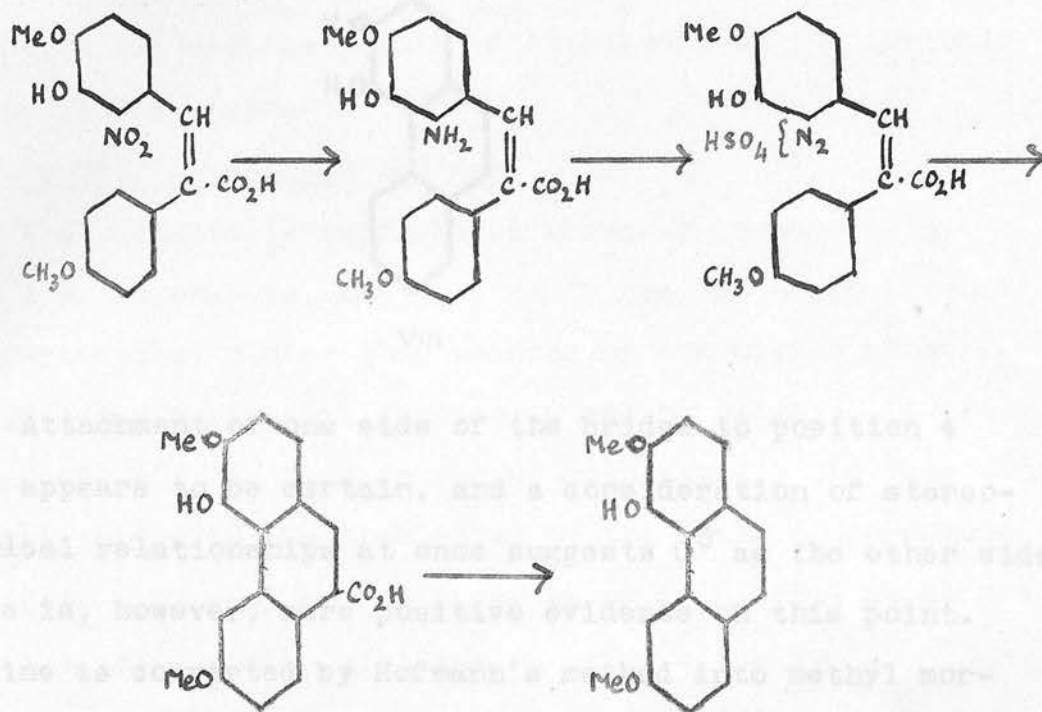
In all these degradations, the group  $-C-C-N$  is liberated, the exact form which it takes depending on the state of oxidation of the derivative and on the reagent used. It must be noted that either (i) the nitrogen atom is set free by itself, as trimethylamine, leaving a vinyl group (morphothebaine) or producing ethylene (methyl-morphenol), or (ii) the side-chain forms compounds in which there is always a carbon chain of two methylene groups (thebaol). The grouping  $\begin{array}{c} | \\ N-CH-CH_3 \end{array}$  does not occur in degradations of morphine products.

C. Of the three oxygen atoms, one is phenolic. It is readily acetylated or benzoylated; it renders morphine soluble in alkali, whereas the methyl ether, codeine, is insoluble; and Chastaing has prepared definite alkaline earth salts, which may be decomposed with carbon dioxide.

The second oxygen atom forms part of a secondary alcoholic hydroxyl group, which may be oxidised to a carbonyl group, and may also be acylated.

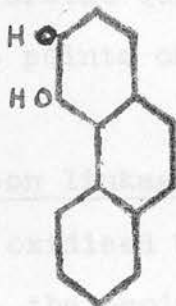
Pschorr and his collaborators have shown conclusively that the positions of these oxygen atoms are 3 and 6 respectively; they have synthesised the methyl ethers of the various phenanthrene derivatives which retain the oxygen atoms. The steps of this noteworthy and valuable

method may be followed best in the accompanying scheme of the synthesis of thebaol from 2-nitrovanillin and p-methoxyphenylacetic acid.<sup>9</sup>



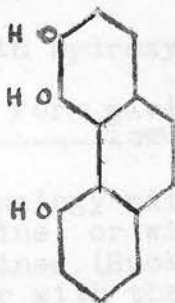
D. The third oxygen atom is non-reactive, and resists the usual methods of characterisation. Under certain conditions of the molecule, however, as for instance a carbonyl group at C<sup>6</sup>, the linkage may be broken, and a phenolic group results. The position of this group<sup>at</sup> C<sup>4</sup> has been definitely shown by the synthesis of morphol (VIII) by Barger,<sup>10</sup> and of its dimethyl ether by Pschorr and Sumuleanu.<sup>11</sup> The second of these compounds is the non-basic product of the action of acetic anhydride on methylthebainonemethine, and thebainone is a ketonic phenol, which is prepared from

codeinone (carbonyl at C<sup>6</sup>) by reducing the oxygen bridge with stannous chloride and hydrochloric acid.



VIII

Attachment of one side of the bridge to position 4 thus appears to be certain, and a consideration of stereochemical relationships at once suggests C<sup>5</sup> as the other side. There is, however, more positive evidence on this point. Codeine is converted by Hofmann's method into methyl morphenol (IV) and the constitution of this substance has been established by the alkaline fusion of morphenol, which produces 3.4.5 trihydroxyphenanthrene (IX). The trimethyl ether of this has been synthesised by Pschorr.



IX

# THE ATTACHMENT OF THE ETHANAMINE

The only controversial questions remaining in the structure (I) are the points of attachment of the two ends of the -C-C-N chain.

## (i) The Nitrogen-carbon linkage.

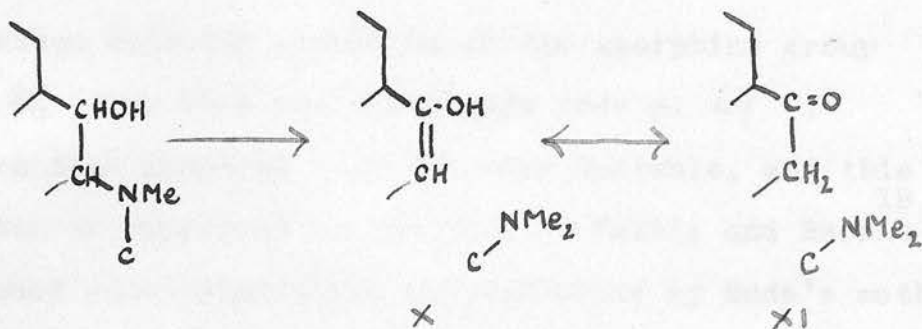
When codeine is oxidised by means of chromic acid at a low temperature, the product is the secondary alcoholic hydroxycodine, richer than codeine by one oxygen atom, and yielding a diacetyl derivative and no oxime.<sup>14</sup> If the methiodide of this base is warmed with alkali, the resulting methine (which is the name given to the class of compounds formed in this way) not only reacts as an alcohol as before, but also as a ketone, yielding an oxime and a semi-carbazone.<sup>15</sup> The normal course of the formation of the methines is to detach the nitrogen atom from the nucleus and form a double bond between the Carbon atoms of the phenanthrene bridge.

Knorr has interpreted these results by locating the new hydroxyl group in hydroxycodine in 9 or 10,<sup>\*</sup> the enolic (X) or ketonic (XI) form giving the characteristic reactions.

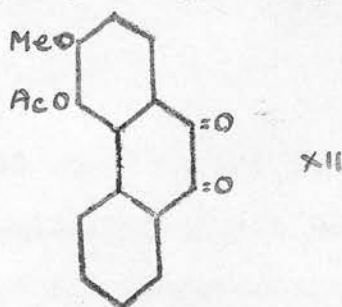
---

\* Probably 10, by analogy with the formation of papaveral-dine from papaverine, or with the oxidation of benzyl-dihydro-isoquinolines (Buck, Haworth, and Perkin J. 1924 125 2176), or with the production of 2'-nitro-6; 3':4' trimethoxy-1-benzoyl.3:4 dihydroisoquinoline (Publication 14).





The placing of the hydroxyl group on one of the bridge carbon atoms is confirmed when the action of acetic anhydride on ketodihydromethylmorphimethine (XI) is considered. The products of this degradation are acetyl-ethanoldimethylamine and a methyldiacetyltrioxyphenanthrene, which is different from that obtained from codeinone by the same reaction<sup>16</sup>. Oxidation of this acetyl derivative with chromic acid yields 3-methoxy 4. acetoxyphenanthrenequinone<sup>17</sup> (XII), one hydroxyl group disappearing.

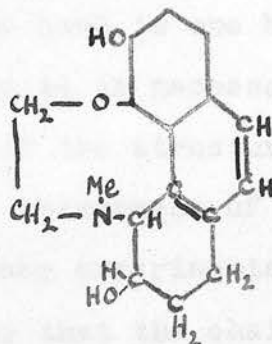
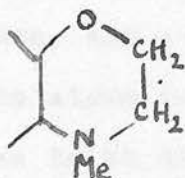


From the evidence described above it is clear that as soon as the nitrogen atom is no longer attached to ring II, keto-enol tautomerism can take place. The nitrogen atom must therefore be linked to the carbon atom in position 9 or 10.

A comparison with the alkaloids of the aporphine group (see p. 82 ) or with morphothebaine (see p. 49 ) indicates that position 9 is the more suitable, and this conclusion is supported by the work of Fattis and Heczko<sup>18</sup> who reduced dimethylmorphine methochloride by Emde's method.

(ii) The Carbon-carbon linkage.

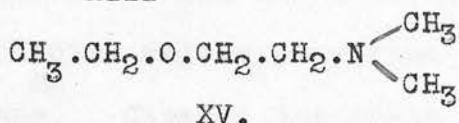
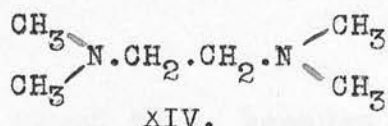
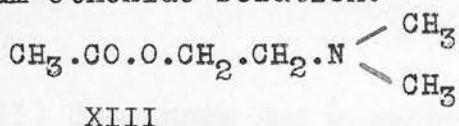
There remains the carbon to carbon linkage of the ethanamine side-chain. The earlier formulae, due to Knorr and Freund, contained an oxazine ring, or even an eight-membered heterocyclic ring.



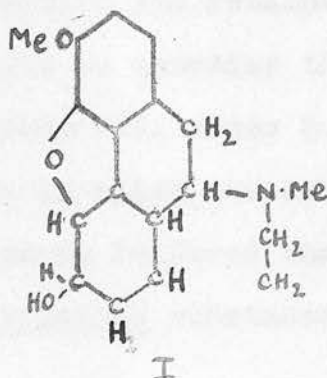
These suggestions owed their existence to the production of acetyethanol-dimethylamine (XIII) and acetyethanol-methylamine in the earlier decompositions of  $\alpha$ -methyl-morphimethine and of thebaine by means of acetic anhydride,<sup>19</sup> and it was not until other reagents were used that it became obvious that the presence of an oxygen atom in these compounds was due to a secondary reaction, - addition to



-  $\text{CH}_2 = \text{CH} - \text{N}$  , the primary product. Thus the action of caustic soda on thebaine methiodide results in the formation of tetramethylethylenediamine (XIV), in which dimethylamine has been added to vinyl-dimethylamine. In the same way, codeinone methiodide and  $\alpha$ -methylmorphimethine yield dimethylamino-ethyl-ether (XV) on boiling with alcohol or sodium ethoxide solution.



It is clear therefore, that the bond is one between two carbon atoms, and at this stage it is necessary to examine each of the atoms in ring III of the structure (I) as regards its fitness to be the point of attachment of the ethanamine chain. From the results of many experiments it may be assumed with complete certainty that the chain is linked to ring III.



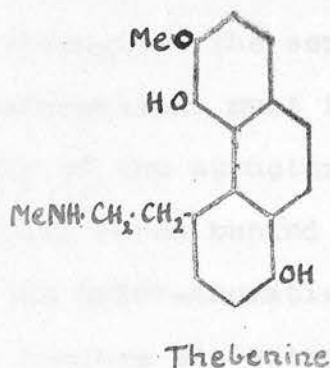
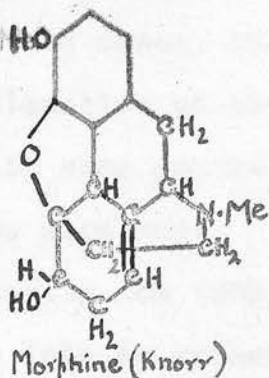
(1) Codeinone has a carbonyl group in 6, because its methiodide may be converted into 3-methoxy-4:6-dioxyphenan-<sup>22</sup>threne. Clearly, the chain cannot be in 6 in this ketone, nor, by implication, in position 6 of the secondary alcohols, codeine and dihydrocodeine.

(2)  $\psi$ -Codeinone has a carbonyl group in 8, because its methiodide may be converted in 3-methoxy-4:8-dioxyphenan-<sup>22</sup>threne. In the change from codeine to  $\psi$ -codeine, which is brought about by the use of boiling dilute sulphuric acid, there occurs a migration of hydroxyl from 6 to 8. This change does not affect the connections of the side chain, since codeine and  $\psi$ -codeine yield the same deoxycodine<sup>24</sup> (-CHOH- reduced to -CH<sub>2</sub>-). Hence the side-chain cannot be attached to position 8.

(3) In 7, there can be no carbon link since the author has proved the existence of a -CO-CH<sub>2</sub> group in dihydrocodeinone (Publication 8), and the reactive methylene-group

in this ketone can only be in position 7, since the substance is non-phenolic and retains the oxygen bridge.

It now remains to consider the case of the remaining carbon atoms of ring III, atoms 5, 13, and 14. Knorr adopted a formula in which the side-chain was attached to 5, chiefly because he believed that it occupied that position in the aromatic substance thebenine. (p. 54).



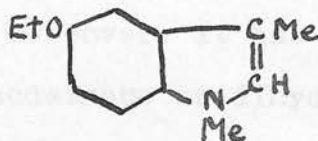
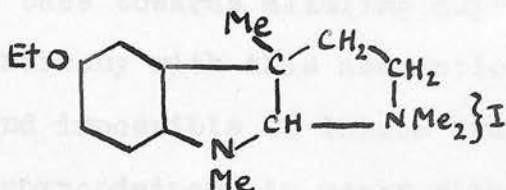
Should Knorr's formula be accepted, difficulties would be experienced in accounting for the behaviour of the isomeric methylmorphimethines. Clearly, two of these (presumably  $\beta$  and  $\delta$ ; see page 33) would be derivatives of naphthalene and therefore benzenoid in their unsaturation, whereas experiment demonstrates convincingly that this is not the case, and that all are aliphatic in character. It is impossible to maintain the accuracy of Knorr's formula in the face of this negative experimental evidence, more

---

1. It has now been shown (Publication 10) that Knorr was justified in his assumption regarding the constitution of thebenine.

especially when such evidence is used to support a theoretical point of considerable importance. Of all the reactions encountered in the chemistry of morphine derivatives, none are more surprising than those in which an aromatic phenanthrene system and an amino-ethanol compound are evolved simultaneously. It is now recognised that such degradations involve the break of a carbon-to-carbon union, and experience has shown that they are by no means confined to isolated cases, but occur throughout the series, and the explanation of these transformations must therefore be sought in some general property of the structure of the morphine alkaloids. The driving force behind the change is evidently the tendency of the hydro-aromatic compound to pass into an aromatic one, because the extrusion of the side-chain is never observed independently of the formation of a true phenanthrene derivative. The obvious conclusion, however, was for long unnoticed. The formation of the aromatic phenanthrene compound cannot take place for structural reasons unless the ethanamine side-chain is displaced in favour of a hydrogen atom or hydroxyl group. To ensure clearness and understanding, the conclusion may be repeated in different words: the carbon-to-carbon attachment of the C-C-N chain forms a direct barrier to the existence of an aromatic phenanthrene, in which it would be retained as a

normal side-chain. It is at once evident that the only condition of structure which could inhibit aromatic-ring formation is the linkage of the end carbon atom of the chain to one of those quaternary carbon atoms (13 or 14), which are common to two nuclei in the resulting phenanthrene derivative. An analogous case is that of abietic acid,  $C_{19}H_{29}COOH$ , which always loses a methyl group when converted to retene,  $C_{18}H_{18}$ , a methyl isopropyl phenanthrene. The accepted explanation of this phenomenon is that the methyl group is attached to a carbon atom which is common to two rings. A similar example is given by the degradation of esetherole methiodide which yields the corresponding indole<sup>25</sup> by loss of an ethanamine chain.



Strangely enough, the same deduction was not drawn with regard to morphine derivatives till 1923 (Publication 1), and none of the formulae which were put forward up till that date satisfy these requirements. The hypothesis which has just been made is obviously of the greatest importance, and from it two lines of enquiry have been developed. Firstly, was it possible to decide experimentally



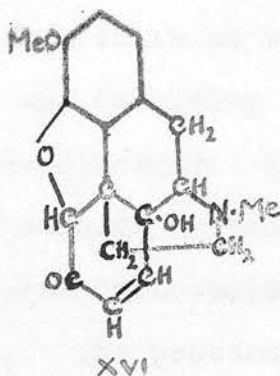
to which of the carbon atoms, 13 or 14, the side-chain was attached; and secondly, could positive experimental evidence (cf. p.14) be obtained that the chain was not linked to position 5?

The first question was decided by a study of the chemistry of hydroxycodeinone and its derivatives (Publications 3 and 8). This ketone is formed by the oxidation of thebaine with hydrogen peroxide, and the change has been represented as the transformation of the group  $-C(OMe)=CH-$  into  $-CO-CHOH-$ . This formulation of hydroxy-codeinone as an  $\alpha$ -hydroxyketone is however, quite unjustified by the evidence and, in particular, the high degree of stability exhibited by the base towards alkaline cupric and silver solutions is not in harmony with this assumption. Moreover, it has been found impossible to induce hydroxycodeinone or dihydrohydroxycodeinone to react with o-phenylene diamine in boiling acetic acid solution, - a reaction which is characteristic of  $\alpha$ -hydroxy ketones. Again, the apparent impossibility of dehydrating hydroxycodeinone and its derivatives negatives the view that this substance is a  $\beta$ -hydroxyketone, and this conclusion has been strengthened by the failure of these bases to react with oo'diaminoveratrone in presence of atmospheric oxygen. \*

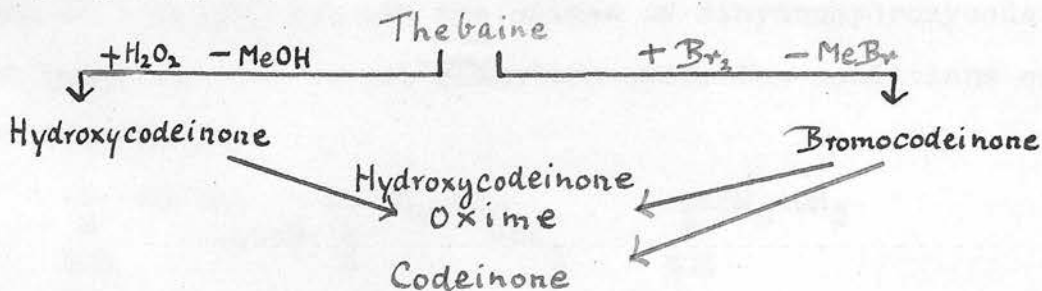
---

\* Diaminoveratrone readily condenses with  $\beta$ -diketones to form naphthyridines. (compare Publication 4).

appear to be possible to construct a thebaine formula which can, in any plausible manner, give rise to a  $\beta$ -hydroxyketone having the composition of hydroxycodeinone. Nothing can be urged, therefore, against the remaining alternative - namely, that hydroxycodeinone is a  $\gamma$ -hydroxyketone, and must be represented by (XVI).



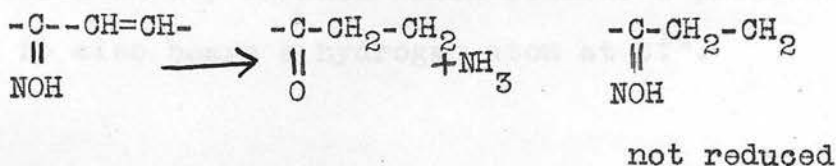
Its relation to codeinone follows from the observations  
 that bromocodeinone and hydroxycodeinone yield the same  
 hydroxycodeinone oxime (Publication 3), and that bromo-  
 codeinone may be reduced to codeinone and to dihydrocodeinone  
 these relationships are most easily understood from the accom-  
 panying diagram.



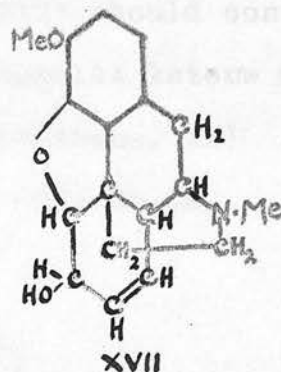
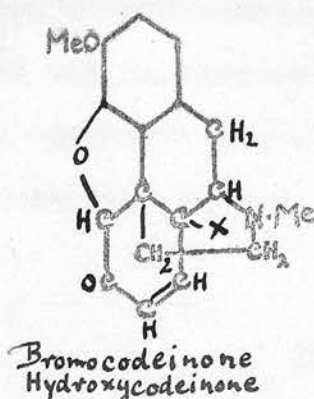
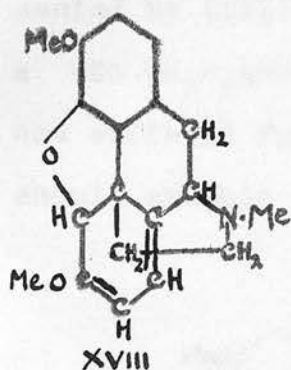
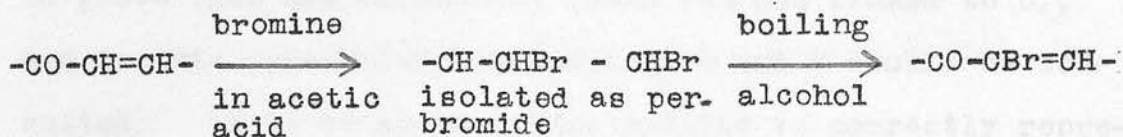
\* A ketone prepared by the bromination of thebaine in acetic acid solution.



The condensations with aldehydes and with 6-aminopiperonal which are described in Publication 3 indicate that dihydrohydroxycodone contains the group  $-\text{CO}-\text{CH}_2-$ , but that this group does not occur in hydroxycodone. These facts are best explained by the presence of the group  $-\text{CO}-\text{CH}=\text{CH}-\text{C}(\text{OH})-$  in hydroxycodone, from which it follows that thebaine contains the group  $-\text{C}(\text{OMe})=\text{CH}-\text{CH}=\text{C}$ , and that the production of hydroxycodone from it is an example of addition to a conjugated system. The following observations must be quoted in support of these conclusions. Schöpf<sup>29</sup> has confirmed the presence of two double-bonds in thebaine by the preparation of a non-phenolic tetrahydrothebaine in the catalytic reduction of the alkaloid. The presence in hydroxycodone of an  $\alpha\beta$ -double-bond which is absent from dihydrohydroxycodone<sup>30</sup> is shown by the work of Speyer and his collaborators, who did not however place this interpretation on their results. When hydroxycodone oxime and benzylideneacetoxime are reduced catalytically, the nitrogen of the oximino-group is eliminated from the molecules as ammonia and the double-bond is reduced, whereas the oximes of dihydrohydroxycodone and benzylacetone resist reduction under the conditions of the experiment.

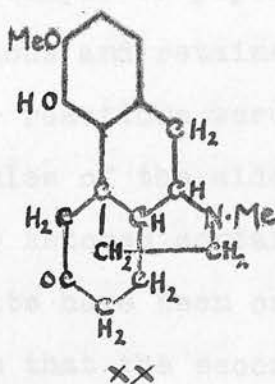
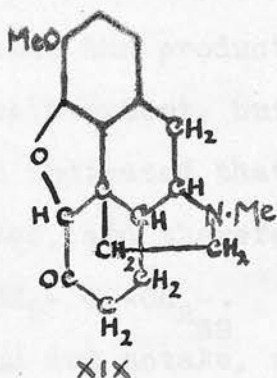


Moreover, the stages of the bromination of the aliphatic part  
<sup>31</sup>  
of the hydroxycodeinone molecule are in harmony with the  
recognised reactivity of the  $\beta$ -bromine in a dibromo-ketone,  
and the reaction may be represented as follows:



From a consideration of the relationships of codeine, bromocodeinone, and hydroxycodeinone which have been indicated above, it is clear that codeine must be represented by (XVII), and that C.<sup>14</sup> must carry a hydrogen atom in codeine and a double-bond in thebaine (XVIII). It follows, therefore, that the only available point of attachment for the ethanamine chain in ring III is C.<sup>13</sup>, and this conclusion is supported by the fact that the isomerisation of  $\alpha$ - and  $\gamma$ -methyilmorphimethines into  $\beta$ - and  $\delta$ -methyilmorphimethines cannot receive a natural explanation in any formula which retains a phenanthrene nucleus unless it also bears a hydrogen atom at C.<sup>14</sup>.

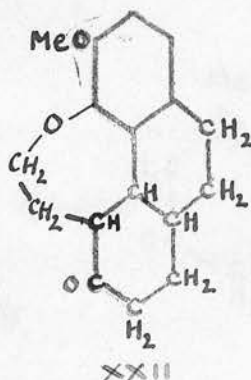
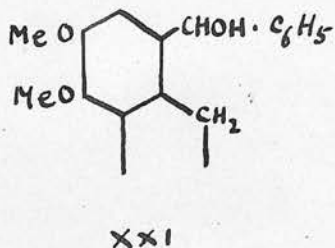
The second field of investigation to be studied in connection with the theory of the inhibition of aromatic ring-formation (p.15) involved a large number of attempts to prove that the ethanamine chain was not linked to C.<sup>5</sup>, and in this connection Publications 2 and 8 should be consulted. If it be assumed that codeine is correctly represented by (XVII), then dihydrocodeinone (XIX) should contain a  $-\text{CO}.\text{CH}_2-$  group and the corresponding phenolic ketone which has suffered further reduction (dihydrothebainone, XX) should exhibit the reactions of the group  $-\text{CH}_2-\text{CO}-\text{CH}_2-$ .



The presence of a reactive methylene group in dihydrocodeinone was readily shown by allowing it to condense with 6-amino-piperonal to form a quinoline-derivative (Publication 8), or by the formation of the vivid red potassium salt of the salicylidene-derivative when a solution of the ketone and salicylaldehyde in alcoholic potash was warmed.

Correspondingly, the reactive methylene group was found to be absent from codeinone, since this substance does not react with aldehydes or nitrosodimethylaniline, and since the colour reactions described in Publication 2 are inconclusive in that they apply equally to a compound with the group  $-\text{CO}-\text{CH}=\text{CH}-$ .

These methods of demonstrating the presence of reactive methylene groups proved less satisfactory when applied to dihydrothebainone (XX). As described in Publication 2, this ketone and its methyl ether, and thebainol and its methyl ether (see p. 42), reacted rapidly with one, but slowly with two molecules of benzaldehyde or piperonal. In each case the product was amorphous and retained water to a certain extent, but the colour reactions were characteristic and indicated that two molecules of the aldehyde had reacted, and therefore that the ketones contained the group  $-\text{CH}_2-\text{CO}-\text{CH}_2-$ . These results have been criticised by Wieland and Kotake, who maintain that the second molecule of the aldehyde has reacted with a nuclear carbon atom of the benzene ring (XXI), and point out that thebenone (XXII according to Wieland and Kotake) reacts with only one molecule of aldehyde or nitrous acid.

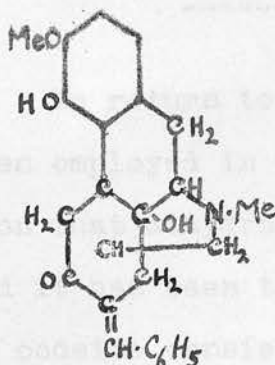


In order to reply to these criticisms the author made a number of attempts both to modify the conditions of the experiments in such a way that crystalline compounds only were employed (Publication 8), and to evolve different methods of investigating the point in question. Since these attempts were all unsuccessful, it will be sufficient to describe one of them, more especially as a modified constitution must now be assigned to two of the compounds which were investigated, namely thebainone and thebainol see p.45). Benzylidenehydroxydihydrothebainone is formed in quantitative yield when dihydrohydroxythebainone is condensed with benzaldehyde in alkaline solution. This substance resisted all efforts to effect further condensation with a second molecule of aldehyde or with 6-aminopiperonal, and the inactivity is clearly due to steric hindrance and is paralleled by that observed in the case of dehydrocholic acid and of the much simpler 3-methylcyclohexanone which forms a monobenzylidene derivative.

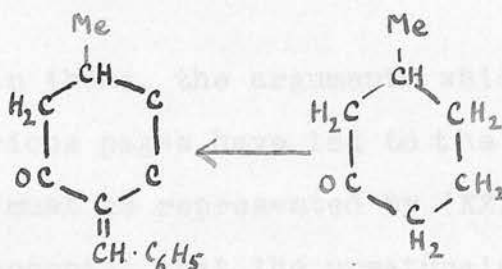
---

\* A product of the reduction of hydroxycodeinone and therefore related to codeinone.





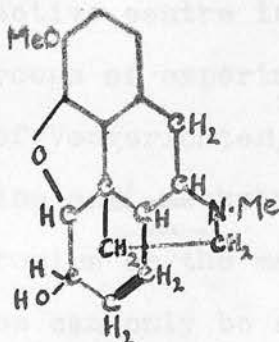
Benzylidenehydroxy dihydrothebaine



35

Schöpf has recently demonstrated in an elaborate but most elegant manner that the ethanamine chain is absent from C<sup>5</sup>, and has consequently proved the truth of the hypothesis of the inhibition of benzenoid character by the presence of the chain (p. 15).

From the whole of the evidence which has been discussed in the preceding pages it follows that dihydrocodeine must be represented by (XXIII).



XXIII

# THE UNSATURATION OF CODEINE

---

To return to the main theme, the arguments which have been employed in the previous pages have led to the conclusion that dihydrocodeine must be represented by (XXIII), and it has been tacitly accepted that the unsaturated centre of codeine consists of a double bond between C<sup>7</sup> and C<sup>8</sup>. This point must now be considered in greater detail, and it will be shown that the assumption of the presence of a double bond in this position is fully justified.

In the first place, it is evident that the codeine molecule contains a centre of reactivity which must be either a double bond or a weak single link. No evidence in support of this statement is required beyond the remarkable ease with which codeine is reduced catalytically to dihydrocodeine,<sup>36</sup> and the formation of dihydroxycodeine by oxidation of the alkaloid by means of very dilute aqueous permanganate.<sup>37</sup> The proof that this reactive centre is a double bond in ring III depends on three groups of experiments:

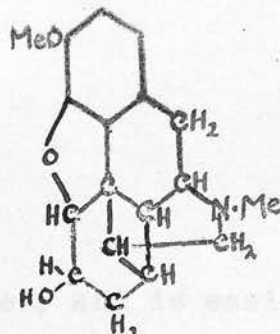
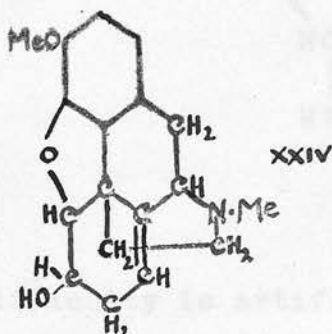
(i) The work of Vongerichten, Hübner and Denmsdorf on the action of bromine on  $\Delta$ -methyilmorphimethine, and of Pschorr on the action of bromine on the methyl ethers of  $\Delta$ - and  $\epsilon$ -methyilmorphimethines can only be explained by the assumption that the halogen attacks an unsaturated centre in ring III. The main object of Pschorr's work, for example, was to alter



the state of oxidation of ring III in such a way that the methoxy-group at C<sup>6</sup> would not be eliminated in the course of the degradation to a non-nitrogenous phenanthrene derivative, and he succeeded in attaining this end.

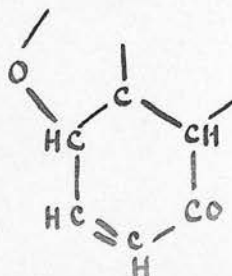
38

(ii) Van Duin, Robinson and Smith have shown that the alkaloid neopine is an isomer of codeine, and consider it to be  $\beta$ -codeine (XXIV) bearing the same relation to codeine that  $\beta$ -methyilmorphimethine does to the  $\alpha$ -isomeride. Neopine is more stable to oxidising and reducing reagents than is codeine, and Van Duin, Robinson, and Smith point out that this difference would be inexplicable if codeine contained a bridge-linkage and neopine a double bond.

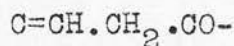
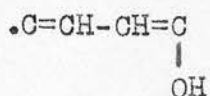
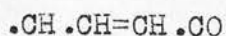


\* These authors suggest that the stability of neopine is the result of the location of the double bond in a more "sheltered" position. They do not consider the possibility that neopine contains no double bond but has a bridge linkage, of the type suggested in Publication I as representing the morphine alkaloids. Such a structure would explain the stability of neopine and might, moreover, have a bearing of considerable importance in connection with the phytochemical relationships of the phenanthrene bases (p.102) The formation of  $\beta$ -methyilmorphimethine by the action of boiling potash on neopine methiodide would then be explained by the break of the unstable bridge and the simultaneous formation of a conjugated system of double bonds.

(iii) The properties of hydroxycodeinone, and probably also of codeinone are those of  $\alpha\beta$ -unsaturated ketones, and since it has been shown (Publication 3 and 8) that the non-phenolic dihydrohydroxycodeinone and dihydrocodeinone both contain a reactive methylene group, it is evident that the formation of the two latter substances by reduction of the two former ones involves the saturation of a double bond between  $C^7$  and  $C^8$ . The objections might be made that codeinone reacts with benzaldehyde and nitrous acid as if it contained the group  $-\text{CH}_2-\text{CO}-$ , whereas on the suggested basis it should be represented by the formula:

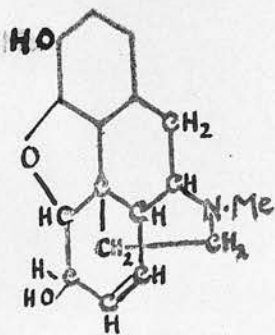


This difficulty is artificial, however, and is easily overcome by recognising the equality of the tautomers:

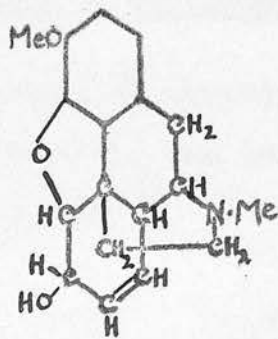


The consideration of the evidence which is available for the selection of a formula to represent codeine is now completed, and from the brief survey which has been given,

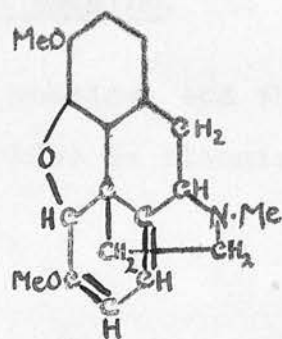
the following formulae for the morphine alkaloids may be deduced.



morphine



codeine

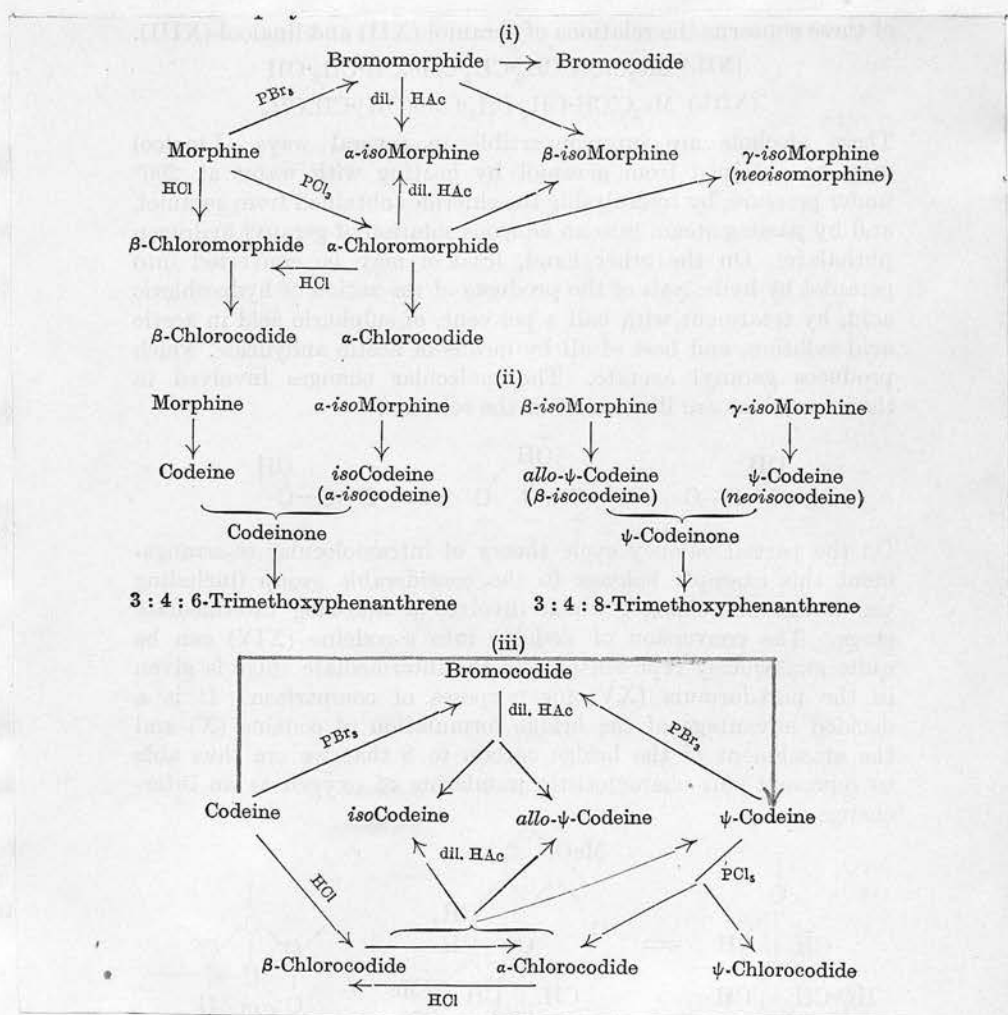


thebaine

# THE SALIENT FEATURES OF MORPHINE CHEMISTRY

## (1) The Isomerides of Morphine and Codeine.

The relation of morphine, codeine, and their halogen derivatives and isomerides is illustrated in the following tables.



Codeine and isocodeine are a pair of stereo-isomerides, in which the secondary alcoholic group is at 6. On oxidation the isomerism vanishes, and both yield the same ketone, <sup>40</sup>codeinone. By heating codeinone with acetic anhydride, <sup>41</sup>or codeinone methiodide with alcohol at 150°, <sup>42</sup>3-methoxy-4:6-dioxyphenanthrene is produced, the oxygen of the keto-group being retained as a hydroxyl in position 6. The constitution of this phenanthrene was established <sup>43</sup>by the synthesis of its dimethyl ether.

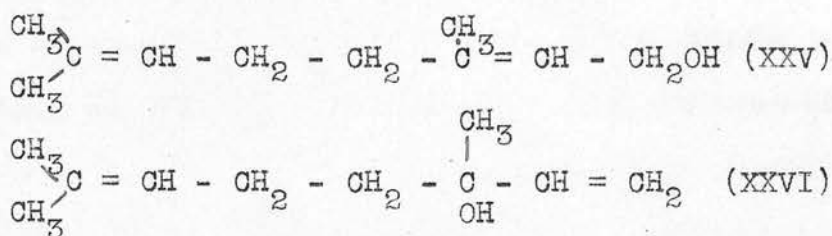
$\psi$ -Codeine and allo- $\psi$ -codeine are also stereo-isomerides, and give rise to the same ketone, <sup>44</sup> $\psi$ -codeinone. The alcoholic group is in position 8, as has been shown by conversion of  $\psi$ -codeinone methiodide to 3-methoxy-4:8-dioxyphenanthrene <sup>45</sup>by heating with alcohol. The dimethyl ether of this phenol has been synthesised by Pschorr <sup>46</sup>and Busch. Although the positions of the alcoholic group in the isomers are indicated in this way with some likelihood of certainty, the unexpected appearance of the keto-group as a hydroxyl makes migration of the oxygen atom a possibility. Other compounds from which information on this point might be gathered are the methines which contain the oxygen atom as a hydroxyl group. Owing to their state of oxidation however, direct degradation causes elimination of the alcoholic group,



$\alpha$ -methylnorphimethine, for example, yielding methyl  
 morphol <sup>47</sup>(V). Nevertheless, if the hydroxyl group of  
 the methines could be retained in the molecule during the  
 degradative process, and the phenol could then be identi-  
 fied, there could be little doubt as to the position of the  
 alcoholic radicle in the original compound. <sup>48</sup>Pschorr  
 was entirely successful in the experiments which he under-  
 took with this aim. He methylated the alcoholic hydroxyl  
 by means of dimethyl sulphate and alkali, and in order to  
 avoid the removal of the  $-OCH_3$  group as methyl alcohol  
 utilised the method of Vongerichten, Hübner, and  
<sup>49</sup>Densdorff, and treated the methine-ether with bromine  
 in acetic acid or chloroform solution. Under these  
 conditions two atoms of bromine are added to the  
 molecule, and one of these is replaced by an acetoxy-  
 or hydroxy group. The methyl ether of bromo-acetoxy-  
 dihydro- $\alpha$ -methyl-morphimethine was decomposed by warm  
 acetic anhydride to 3:6-dimethoxy-4-acetoxyphenanthrene,  
 whilst the methyl ether of bromo-oxy-dihydro- $\epsilon$ -methyl-  
 morphimethine led to 3:8-dimethoxy-4-acetoxyphenanthrene  
<sup>50</sup>under the same conditions. The constitution of these  
<sup>51</sup>substances has been definitely established by synthesis.  
 These reactions decide conclusively the position of the  
 alcoholic radicle in the various isomerides - namely 6  
 in the codeine series, 8 in the  $\psi$ -codeine series.



In the halogeno-morphides and codides the halogen atom replaces the hydroxyl group, but it is not known to which of the two series the halide derivatives belong. They are formed from either pair of structural isomerides, and their hydrolysis with dilute acetic acid leads to a mixture of morphines, or codeines, of both series. This migration of the hydroxyl from an  $\alpha$ - to a  $\gamma$ -position occurs frequently, and it is a reversible process. Perhaps the best known analogous transformations are those concerning geraniol (XXV) and linalool (XXVI) which are interconvertible in several ways



The molecular changes here involved are illustrated by the scheme:-



and the reversible conversion of codeine to  $\psi$ -codeine is an analogous reaction which thus receives a simple explanation. Confirmation of these views on the structure of the isomeric codeines is obtained from a consideration of their behaviour and that of their

isomeric methines when submitted to catalytic reduction. Codeine and isocodeine, and the corresponding  $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\delta$ -methyilmorphimethines, yield non-phenolic dihydro-derivatives (neglecting the additional double bond of the methines whereas the reduction of  $\psi$ -codeine, allo- $\psi$ -codeine, and  $\zeta$ - or  $\epsilon$ -methyilmorphimethines leads to phenolic tetrahydroderivatives in which the oxygen bridge has been ruptured. This variation in properties can only be explained by the assumption that in the second division of compounds the group  $-O-CH=CH-$  reacts as a conjugated system which does not exist in the first division. This behaviour brings these changes into line with the increasing number of examples in which the lone pairs of electrons of nitrogen or oxygen atoms can function as the reactive parts of such structures.

(ii) The Isomeric Methyilmorphimethines.

these substances are obtained by the decomposition

of the codeine ( $\psi$ -codeine) methohydroxides, but they may also be produced by methylating the corresponding morphine derivative. Each of the four codeines gives rise to a different methylmorphimethine. Those derived from codeine and isocodeine may be converted into isomerides by the action of alcoholic alkali, or by other reagents, whereas those corresponding to allo- $\psi$ -codeine and  $\psi$ -codeine do not isomerise.<sup>53</sup>

The following table exhibits the relations and nomenclature of the six methylmorphimethines:-

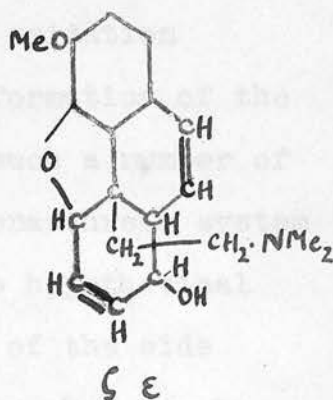
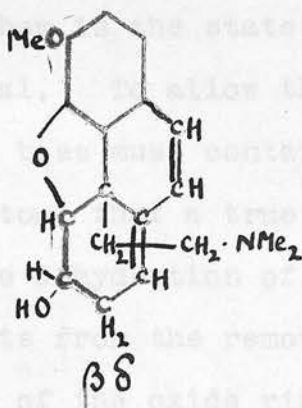
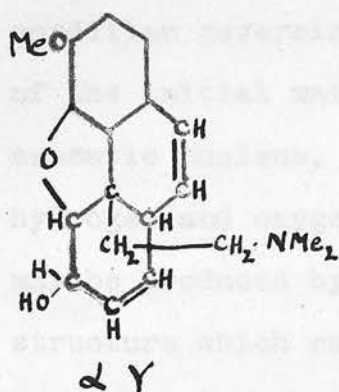
Methohydroxide from			
Codeine	Isocodeine	Allo- $\psi$ -Codeine	$\psi$ -Codeine
$\alpha$	$\gamma$	$\zeta$	$\epsilon$
$\downarrow$	$\downarrow$		
$\beta$	$\delta$		

methylmorphimethine.

It has been clearly demonstrated that the hydroxyl group is at 6 in  $\alpha$ ,  $\beta$ ,  $\gamma$ - and  $\delta$ -methylmorphimethines, and at 8 in the  $\zeta$ - and  $\epsilon$ -isomerides. The group thus forms three pairs of stereo-isomers,  $\alpha$ - and  $\gamma$ - ,  $\beta$ - and  $\delta$ - ,  $\zeta$ - and  $\epsilon$ -methylmorphimethines.

The codeine formula (p. 28) allows the changes under the influence of alcoholic alkali to be explained in a simple manner, the  $\beta\delta$ -molecule consisting of a conjugated system, more stable than the non-conjugated structure of

the  $\alpha\gamma$ - molecule.  $\epsilon$ - and  $\zeta$ -methylmorphimethines receive the formula given below and the stability of these compounds to alcoholic potash is easily understood, when it is observed that the formation of a conjugated system is impossible.



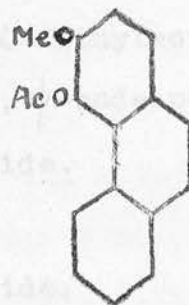
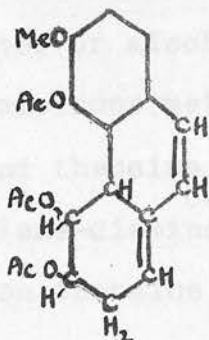
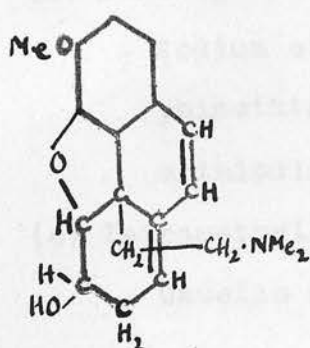
It should be noted that these formulae fulfil one very important condition, namely that by the presence of the CCN chain ring II is prevented from becoming aromatic in character and this is in harmony with the observation that the six methylmorphimethines may all be reduced catalytically to tetrahydro-derivatives and contain one benzenoid ring only.

(iii) Degradations to Aromatic Non-nitrogenousDerivation of Phenanthrene

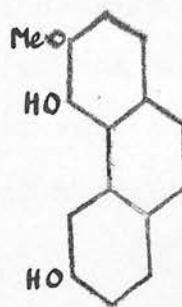
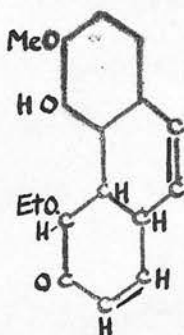
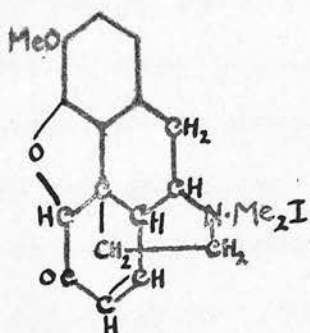
These fissions of the alkaloidal molecule take place under a variety of circumstances, and the only condition governing them is the state of oxidation of the initial material. To allow the formation of the aromatic nucleus, the base must contain such a number of hydrogen and oxygen atoms that a true phenanthrene system may be produced by the dehydration of the hypothetical structure which results from the removal of the side chain and the opening of the oxide ring by what may be termed hydrolysis. Consequently, the form of the aromatic nucleus is restricted to morphol (which may be methylated or acetylated) or to a hydroxymorphol, in which the hydroxyl is in position 6 or 8. An example of each main type of reaction will suffice; the stages represented are, of course, purely hypothetical.

1. The action of acetic anhydride on  $\alpha$ -methyldormorphine. A by-product of this reaction is the acetyl-derivative of  $\beta$ -methyldormorphine, showing that in all probability the first stage is the migration of the double-bond of ring III to the conjugated position.





ii. The action of alcohol on codeinone methiodide.



A wider latitude is possible, however, in the form in which the side chain is removed, as is shown by the following list.

(a) Acetoxy-ethyl-dimethylamine: <sup>54</sup>

Acetic anhydride on  $\alpha$ -methylmorphimethine and methyl thebainone methine.

(b) Acetoxy-ethyl-methylamine: <sup>55</sup>

Acetic anhydride on thebaine and codeinone.

(c) Chloro-ethyl-dimethylamine: <sup>56</sup>

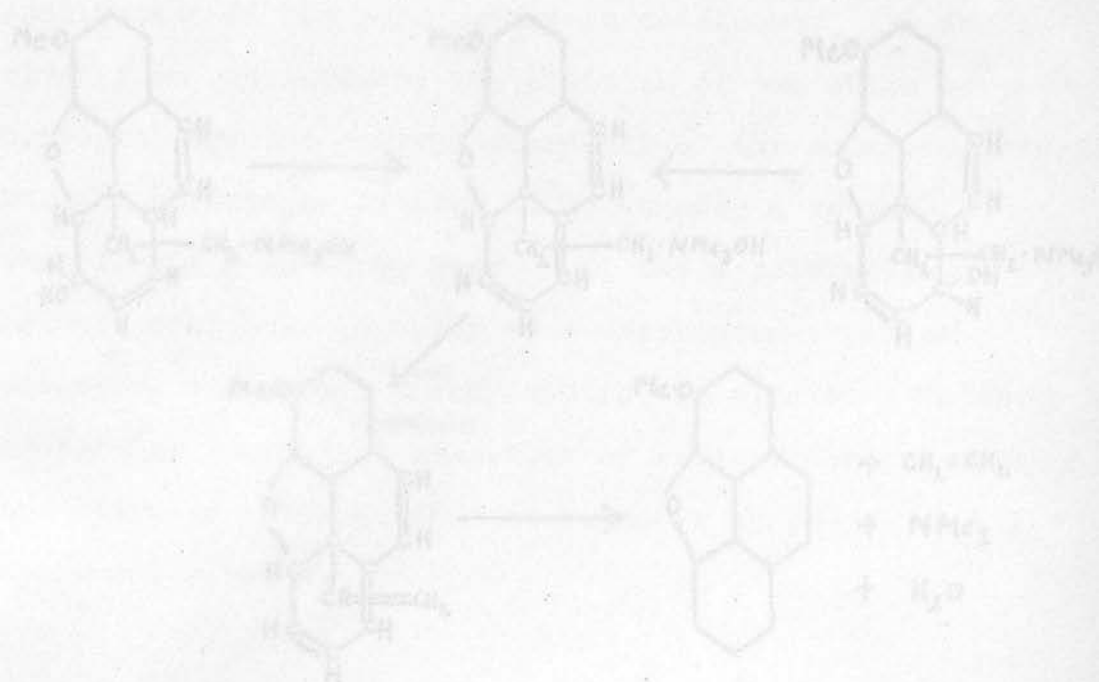
(1a) Hydrochloric acid gas on  $\alpha$ -methylmorphimethine.  
57

(d) Dimethylamino-ethyl-ether:

Sodium ethoxide, or alcohol, on  $\alpha$ -methylmorphimethine, codeinone methiodide,  $\psi$ -codeinone methiodide, and thebaine methiodide.

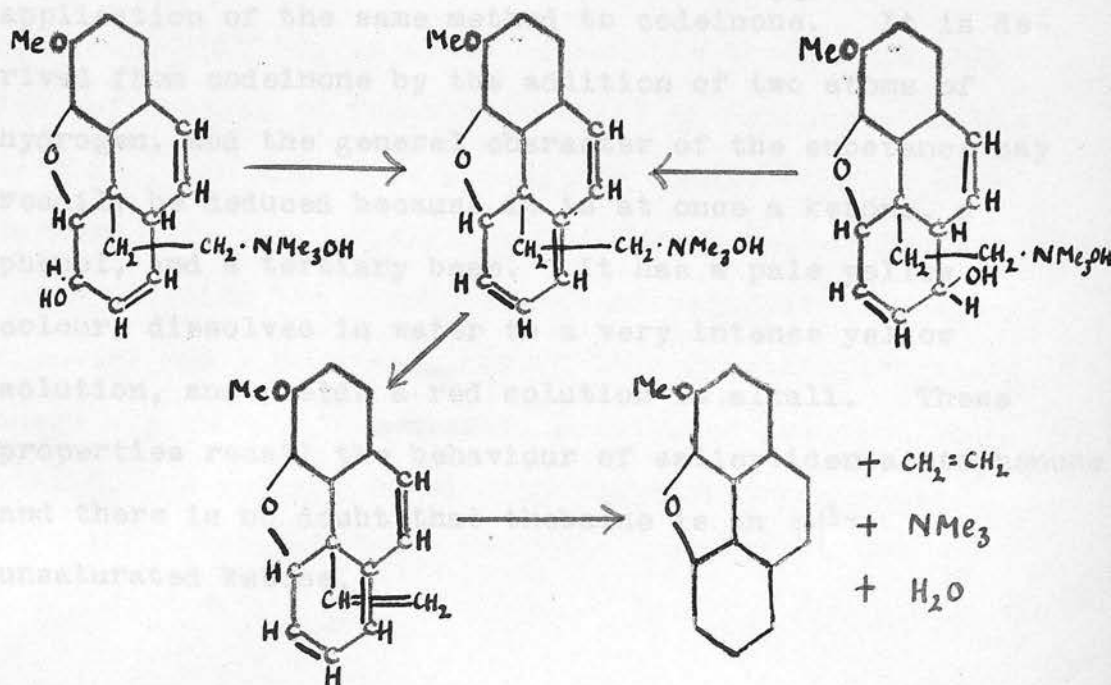
58  
(e) Tetramethyl-ethylene-diamine:

Caustic soda on thebaine methiodide.



(iv) The Production of Methyl Morphenol from the  
Methylmorphimethine

The state of oxidation of a tertiary base is increased by its conversion into a methohydroxide; and the methylmorphimethine methohydroxides are, for this reason, able to change into an aromatic compound, methyl morphenol, without the opening of the oxide ring. The amount of methyl morphenol produced from  $\alpha$ -methylmorphimethine is extremely poor, whereas excellent yields are obtained by using the  $\beta$ - or  $\epsilon$ -isomerides. There is as yet no conclusive explanation of this somewhat strange difference, although it undoubtedly depends on the structural condition of the molecule. It may be governed by the presence, or ease of formation, of a double bond in the 8-14 position.

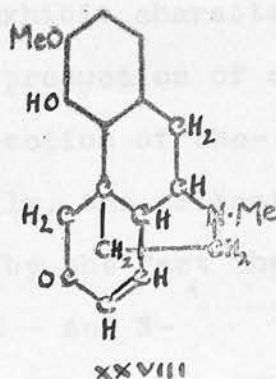
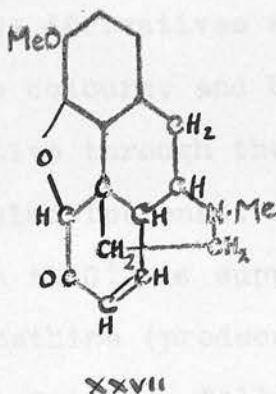
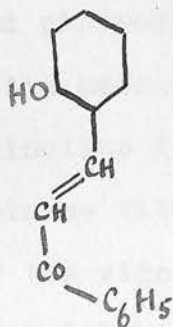


THE ACTION OF ACIDS ON THEBAINE. THE FORMATION OF  
THEBAINONE, MORPHOTHEBAINE, AND THEBENINE.

It has been shown by Knorr that the hydrolysis of thebaine for a few moments with warm dilute acid removes the aliphatic methoxyl group and yields codeinone, and, since this ketone may be substituted for thebaine in any of the reactions which are under consideration, it seems probable that the first action of an acid on the alkaloid is to produce codeinone.

Thebainone

Thebainone is an isomeride of codeine which was first prepared by Pschorr Pfaff, and Herrschmann by the reduction of thebaine by means of stannous chloride and hydrochloric acid at 100°, and later by Knorr by the application of the same method to codeinone.<sup>60</sup> It is derived from codeinone by the addition of two atoms of hydrogen, and the general character of the substance may readily be deduced because it is at once a ketone, a phenol, and a tertiary base. It has a pale yellow colour, dissolves in water to a very intense yellow solution, and yields a red solution in alkali. These properties recall the behaviour of salicylideneacetophenone and there is no doubt that thebaine is an  $\alpha\beta$ -unsaturated ketone.<sup>61.</sup>

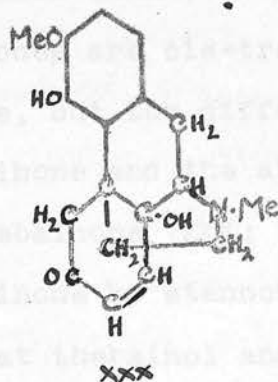
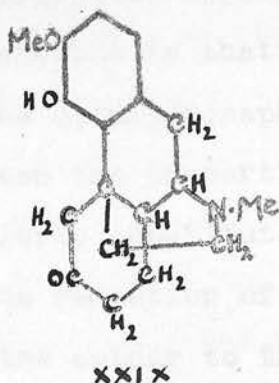


The production of thebainone from codine<sup>e</sup> evidently involves the opening of the oxide ring by reduction and in consideration of the formula assigned to codeinone (XXVII), it seems reasonable to enquire into the suitability of formula (XXVIII) as representing thebainone. In the first place, the double bond is conjugated with the carboxyl group, though not entirely analogous with the ethenoid link of salicylideneacetophenone, and a substance having this constitution might therefore be expected to form a coloured solution in alkali. A comparison with hydroxythebainone shows that this supposition is correct. Secondly, the



formula under consideration demands the presence of a  $\text{CO} - \text{CH}_2 -$  group, and the existence of this structure has been demonstrated experimentally (publications 2 and 8) by the preparation of crystalline benzylidene and piperonylidene derivatives which exhibit characteristic halochromic colours, and by the production of a quinoline derivative through the interaction of thebainone with 6-aminopiperonal. Finally, the allocation of the side chain to  $\text{C}^{13}$  is supported by the fact that methylthebainonemethine (produced by O - and N-methylation of thebainone, followed by the action of alkali) may readily be degraded to methylmorphol and acetyl-ethanoldimethylamine. This elimination of the side chain indicates that it is a barrier to the formation of the aromatic phenanthrene, and thus formula (XXVIII) would appear to represent thebainone in a satisfactory manner. When thebainone is reduced in aqueous solution by means of sodium amalgam (Publication 2, p. 999), the orange colour of the liquid is discharged, and a dihydro-derivative is formed. This substance was first prepared by Pschorr and regarded by him as the secondary alcohol related to thebainone, and hence named thebainol. It is in reality, however, a saturated, phenolic, tertiary-basic ketone, which melts at  $135-136^\circ$

is dextrorotatory and yields a semicarbazone<sup>m.h.</sup> 215-216°. It is therefore derived from thebainone by the addition of two atoms of hydrogen to the double bond, and may for the moment be regarded as (XXIX).

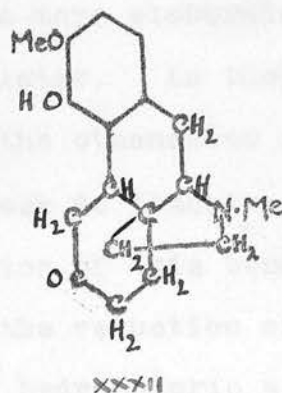
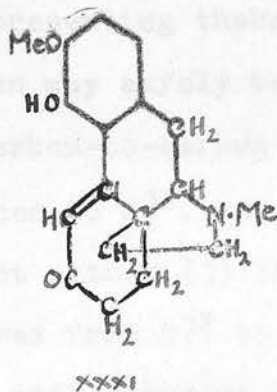


And isomeride of thebainol - unfortunately named dihydrothebainone - had been prepared by Freund,<sup>62</sup> Speyer and Guttmann, and in a purer condition by Skita,<sup>63</sup> Nord, Reichert, and Stukart, by the reduction of thebaine in acetic acid solution by means of hydrogen in presence of palladium or platinum. This ketone

melts at  $137-138^{\circ}$ , is phenolic and tertiary basic, but it is laevorotatory, whereas thebainol is dextro-rotatory. Its semicabazone melts at  $225-226^{\circ}$ , and a mixture with thebainol semicarbazone at about  $205^{\circ}$ . It is clear therefore that the two ketones are quite distinct, yet both are derived from thebaine by reduction and might therefore be represented by formula (XXIX). A possible explanation is that the two ketones are cis-trans isomers of the decahydronaphthalene type, but the differences between the properties of thebainone and the apparently similarly constituted hydroxythebainone (XXX; prepared by the reduction of hydroxycodeinone by stannous chloride) led the author to the belief that thebainol and dihydrothebainone are structural isomerides. Stated briefly, these variations may be summarised as follows: Thebainone gives a marked red halochromic colour in concentrated hydrochloric acid, whereas hydroxythebainone does not. Thebainone sodium salt is red whilst that of hydroxythebainone is yellow. Hydroxythebainone is readily reduced by catalytic hydrogen forming dihydrohydroxythebainone. The double bond of thebainone, however, cannot be reduced under normal catalytic conditions. Some years ago, the author made many attempts to reduce

thebainone in this way, but obtained no indications that reduction took place. The non-reactivity is even more marked in the case of benzylidenethebainone (Publication 8) this is reduced catalytically to a mixture of benzylthebainones, which retain the double-bond of thebainone, but these bases strongly resist further reduction either catalytically or by means of sodium amalgam. It is clear, therefore, that the double bond of thebainone and hydroxythebainone cannot be similarly situated. Now, hydroxythebainone undoubtedly contains the double bond between C<sup>7</sup> and C<sup>8</sup>, and since thebainone is also an  $\alpha\beta$ -unsaturated ketone, it follows that the unsaturated linkage in thebainone must be in the 5-13 position. The consequences of this decision are that the carbon-to-carbon linkage of the ethanamine chain in thebainone must rest on carbon atom 14, since the original assumption must not be forgotten that this linkage inhibits aromatic ring formation (p. 15). Thebainone and thebainol therefore receive the formulae (XXXI) and (XXXII) respectively, and confirmation of the difference between thebainone and hydroxythebainone is obtained by the author's observations that thebainone reacts with o-aminobenzaldehydes (Publication 2), whereas

hydroxythebainone does not, presumably because the methylene group is in the sheltered position (cf. p. 23).



The author had arrived at these conclusions and intended making a publication on the subject, when he was fore-  
 stalled by Schöpf and Borkowsky who propounded the  
 same ideas, and were able to adduce further experimental  
 evidence that dihydrothebainone and thebainol are not  
 cistrans isomerides. They have isolated the oxime of  
 dihydroepithebainone (stereoisomeric with dihydro-  
 thebainone about 0.4%) from the products of the catalytic  
 reduction of thebaine using palladinised calcium car-  
 bonate as a catalyst, and this substance is different  
 from dihydrothebainone oxime or thebainol oxime.  
 Were it not for the difference in structure between

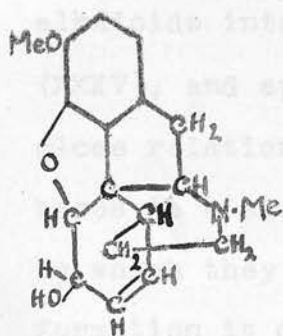


thebainone and dihydrothebainone, there would be three stereoisomers where theory allows only two.

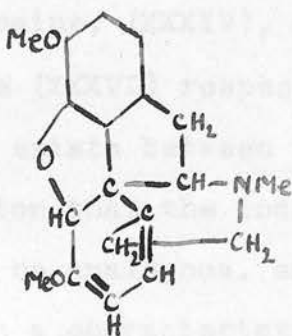
It is necessary to mention briefly the implications which are involved in the recognition of formula (XXXI) as representing thebainone, but a more elaborate discussion may safely be left till later. In thebainone the carbon-to-carbon linkage of the ethanamine chain is attached to C.<sup>14</sup>, and referring back to thebaine, it is evident either (1) that a migration of this bond has occurred from C.<sup>13</sup> to C.<sup>14</sup> during the reduction of thebaine with stannous chloride and hydrochloric acid, or (2) that no migration has occurred and that the ethanamine chain in thebaine (and also morphine) is attached to C.<sup>14</sup> and not C.<sup>13</sup> as previously suggested (p. 24). If the second view is correct and it has both advantages and disadvantages - it must be remembered that C.<sup>14</sup> must carry a hydrogen atom in codeinone in order to allow the formation of 14-hydroxycodeinone, and this requirement can only be fulfilled by abandoning the time-honoured phenanthrene nucleus for a labile ring system (hydrindane derivative, XXXIII) in which a five-membered carbocyclic ring can, when necessary, pass into the isomeric phenanthrene derivative.

---

\* This view has also been suggested by Schöpf (loc.cit.)



Codeine

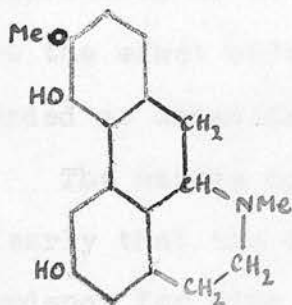


thebaine

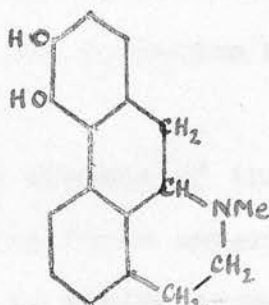
XXXIII

Morphothebaine, Apomorphine, and Apo- $\psi$ -codeine

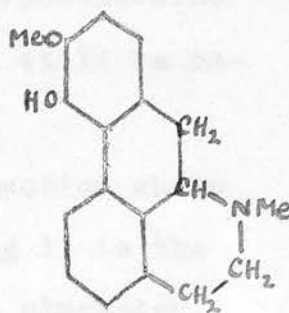
The action of hot concentrated hydrochloric acid on thebaine, <sup>65</sup> morphine, <sup>66</sup> or codeine <sup>67</sup> converts these alkaloids into morphothebaine, (XXXIV), apomorphine (XXXV), and apo- $\psi$ -codeine (XXXVI) respectively, and the close relationship which exists between these aporphine bases is a clear indication that the individual mechanisms by which they arise must be analogous, and that their formation is dependent on a characteristic property of the group as a whole. The author has chosen to discuss the question of morphothebaine, but what follows must apply (with the necessary alterations) to apomorphine and  $\psi$ -apocodeine.



XXXIV



XXXV



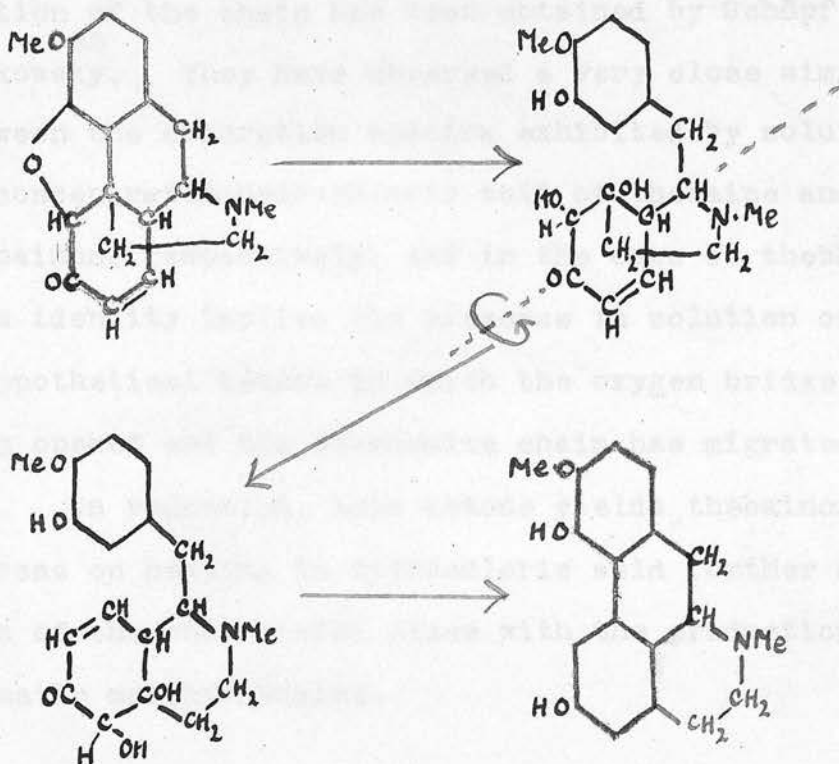
XXXVI

The constitution of morphothebaine has been ascertained by degradation and by synthesis. Pschorr, in his

classical researches on the constitutions of these bases, removed the nitrogen atom from morphothebaine dimethyl ether by exhaustion methylation, and oxidised the resulting vinyl group to carboxyl. By using the method of Curtius he was able to transform this acid into an amino-phenanthrene, which yielded a phenol when diazotised; the methyl ether of this was identical with 3:4:6:8 tetramethoxyphenanthrene which Pschorr synthesised by his method (see p. 7). The synthesis of morphothebaine dimethyl ether has been accomplished by the author and is described in Publication 14; it has a special interest in being the first synthetical production of a basic derivative of morphine. No doubts can therefore be entertained as to the constitution of morphothebaine but the exact mode of its formation must still be regarded as undecided.

The nature of the product of the reaction shows clearly that the driving force underlying it is the tendency for Ring III to assume aromatic character, a condition which can only be obtained by transference of the ethanamine chain from one of the "shared" carbon atoms to an "unshared" atom of ring III - actually C<sup>8</sup>. This may be brought about in two ways; (1) by fission

of the bond 12-13, followed by the rotation of ring III through  $180^\circ$  about the axis 6-14, and attachment of the unsaturated carbon at 8 to position 12; (ii) by migration of the carbon linkage of the side chain.



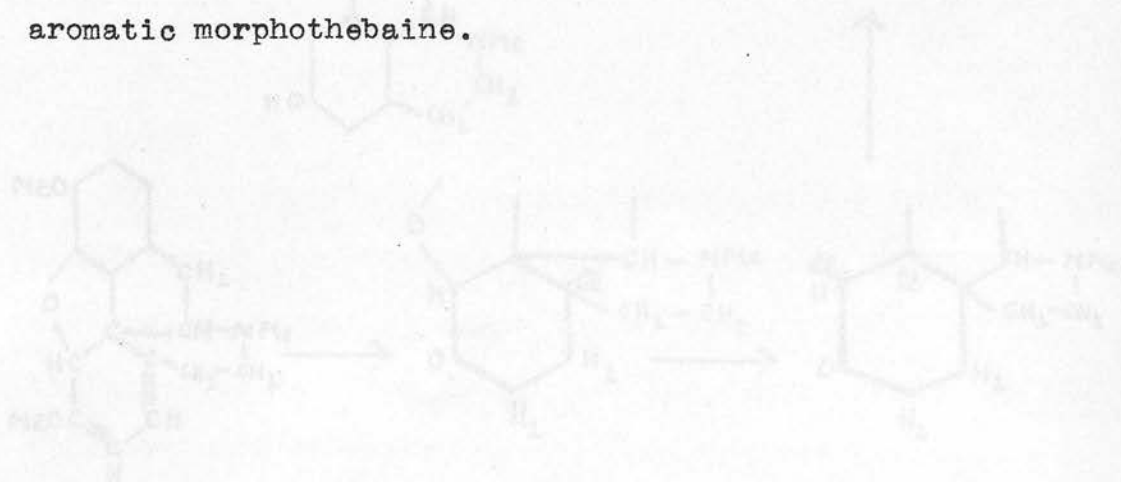
The mechanism required by scheme I is drastic, though  
 suggestive in the way in which it brings out the  
 phyto-chemical relationship with papaverine, and it is  
 remarkable that the formation of morphothebaine is one

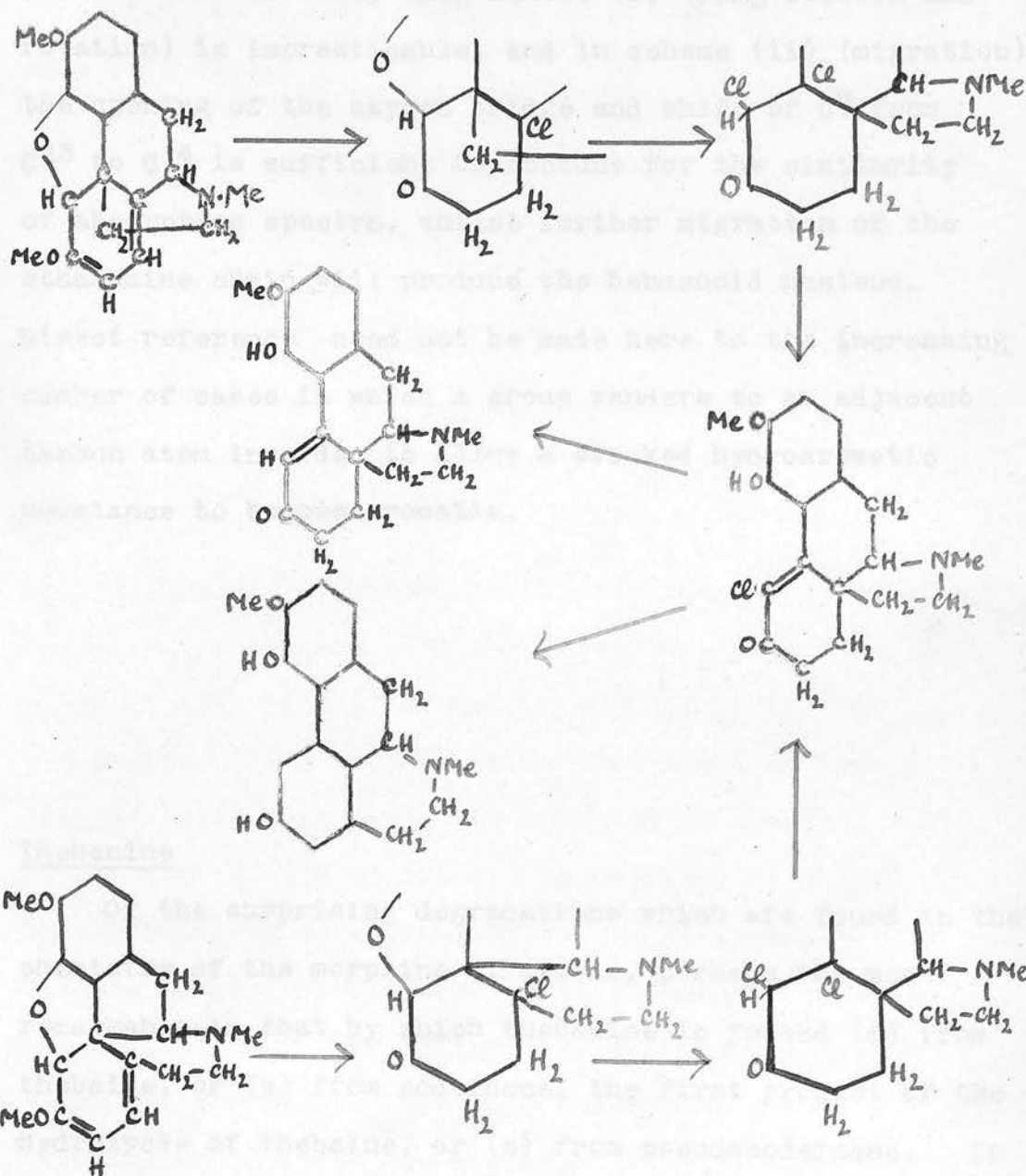
\* Nevertheless, examples are known in which the central bond of phenanthrene nucleus breaks under violent conditions. (compare p.93 ).





of the smoothest processes in the chemistry of the morphine alkaloids. The less vigorous changes involved in migration (scheme II) are therefore more attractive, and definite experimental evidence of migration of the chain has been obtained by Schöpf and Borkowsky.<sup>68</sup> They have observed a very close similarity between the absorption spectra exhibited by solutions in concentrated hydrochloric acid of thebaine and thebainone respectively, and in the case of thebaine this identity implies the presence in solution of a hypothetical ketone in which the oxygen bridge has been opened and the ethanamine chain has migrated to C14. On reduction, this ketone yields thebainone, whereas on heating in hydrochloric acid further migration of the chain takes place with the production of the aromatic morphothebaine.



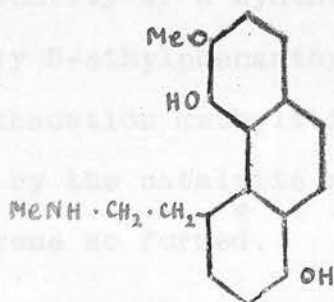


It should be noted that if the thebaine-morphothebaine change be examined by means of the "hydrindane" formula for thebaine, then scheme (i) (ring-fission and rotation) is impracticable, and in scheme (ii) (migration) the opening of the oxygen bridge and shift of C<sup>9</sup> from C<sup>13</sup> to C<sup>14</sup> is sufficient to account for the similarity of absorption spectra, whilst further migration of the ethanamine chain will produce the benzenoid nucleus. Direct reference need not be made here to the increasing number of cases in which a group wanders to an adjacent carbon atom in order to allow a blocked hydroaromatic substance to become aromatic.

### Thebenine

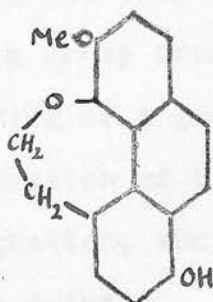
Of the surprising degradations which are found in the chemistry of the morphine alkaloids, perhaps the most remarkable is that by which thebenine is forced (a) from thebaine, or (b) from codeinone, the first product of the hydrolysis of thebaine, or (c) from pseudocodeinone. In the cases (a) and (b) the conversion readily takes place <sup>69</sup> On heating for a few minutes with dilute hydrochloric acid, whereas in (c)

the change is much less facile and boiling acetic anhydride is necessary.<sup>70</sup> The product contains an aromatic phenanthrene nucleus in which the ethanamine groups of the parent substance is present in the form of a side chain.

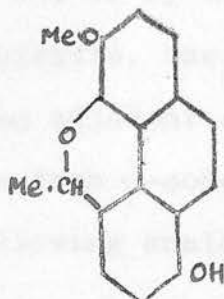


The researches of Pschorr and his collaborators have demonstrated conclusively the position occupied by the methoxyl and hydroxyl groups of thebenine,<sup>71</sup> but the allocation of the side chain to position 5 was based on less definite evidence. It depended on the fact that the product of the exhaustive methylation of thebenine is thebenol, in which the initial vinyl group has reacted further with one of the hydroxyls. Pschorr showed that it is the hydroxyl at 4 and not that at 8 which is involved in this ring formation, and he assigned to thebenol the formula (XXXVII).

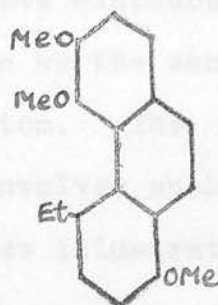
In view, however, of the ease of formation and stability of six-membered oxide rings, the author prefers to adopt the formula (XXXVIII). The final link in the chain of evidence as regards the constitution of thebenine has now been provided (see Publication 10) by the proof of the identity of a synthetical specimen of 3:4:8-trimethoxy 5-ethylphenanthrene (XXXIX) with one obtained by the exhaustion methylation of thebenine dimethylether followed by the catalytic reduction of the vinyl-phenanthrene so formed.\*



XXXVII



XXXVIII



XXXIX

---

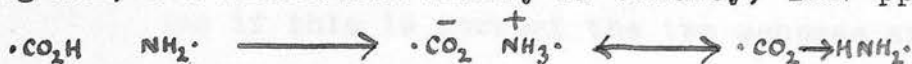
\* In the earlier experiments designed to obtain this proof, attempts were made to convert thebenine into 3:4:5:8 tetramethoxyphenanthrene. These were however unsuccessful, as is described in publication 10, but the necessary tetramethoxyphenanthrene had already been prepared from 2-amino-3:4:2':5'-tetramethoxy- $\alpha$ -phenyl-cinnamic acid (see publication 12). During these experiments, a remarkable isomerism was observed which appears to be characteristic of the trans-2-amino- $\alpha$ -aryl-cinnamic acids. These acids exist in two interconvertible forms: A, which is yellow and unimolecular; B, which is colourless

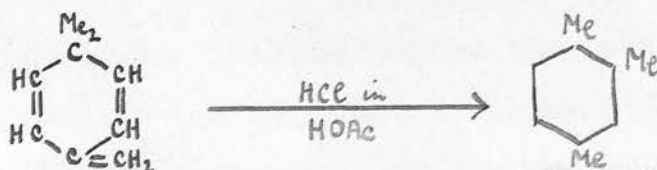


The intramolecular changes which are involved in the formation of thebenine are clearly of the greatest interest when it is remembered that the base is formed from codeinone (CO at 6) and from  $\psi$ -codeinone (CO at 8), all the more because the reaction is extremely facile in the former case and somewhat difficult to accomplish in the latter. It is convenient to consider first the formation from  $\psi$ -codeinone in which the oxygen is already in the correct position in ring III. There are two ways in which blocked hydroaromatic substances having a suitable state of oxidation are known to pass into aromatic compounds. One is by the complete displacement of a group from the molecule, the other is by the wandering of a group to an adjacent carbon atom. The formation of thebenine from  $\psi$ -codeinone involves such a migration, and the following analogous case illustrates the point:-

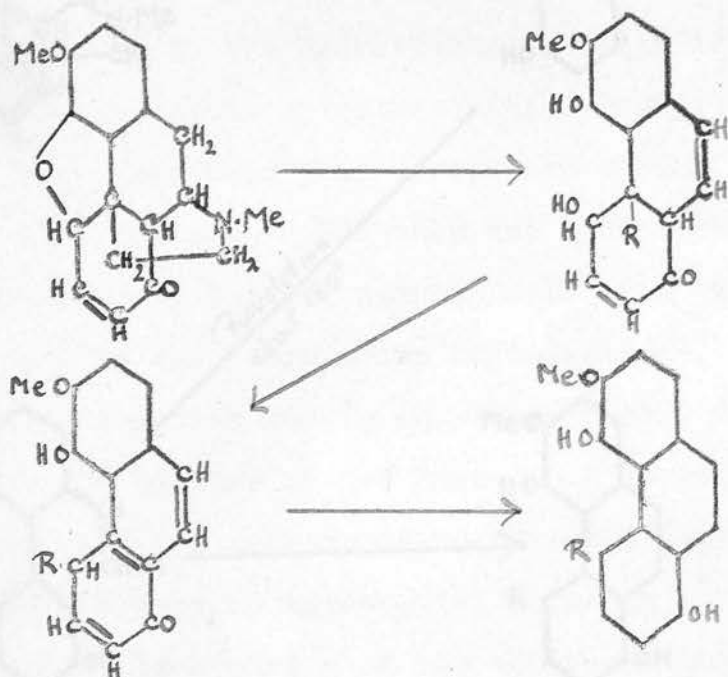
-----  
footnote continued.

and bimolecular. In acid or alkaline solutions, the unimolecular type predominates, whilst in neutral solution the bimolecular is the stable form, and the question is discussed in some detail in publication 12. No conclusion however is made there as to the nature of the isomerism, but the author suggests tentatively that the unimolecular form is the normal amino-acid, whereas the bimolecular form is a salt (formed by the carboxyl of one molecule and the amino-group of the other) in which the initial electrovalency has been replaced by a covalency (compare Sidgwick, The Electronic Theory of Valency, 1927 pp.92-98).

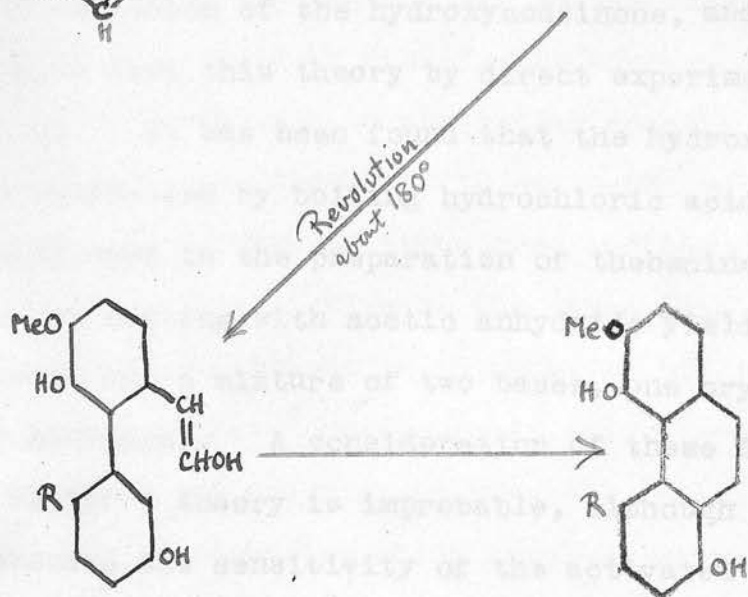
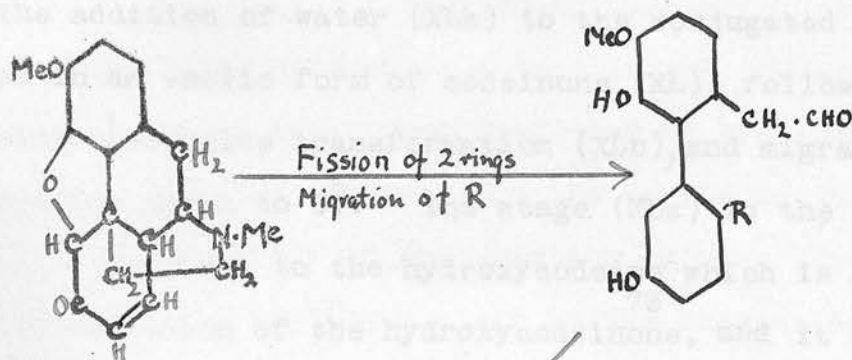




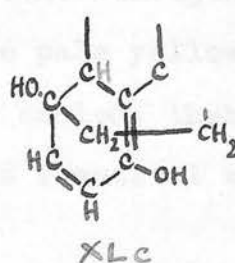
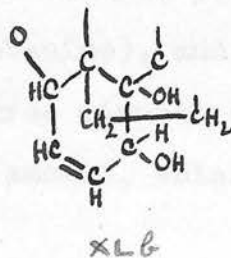
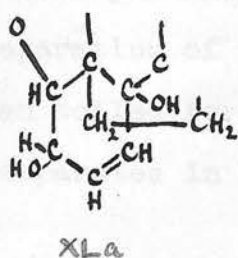
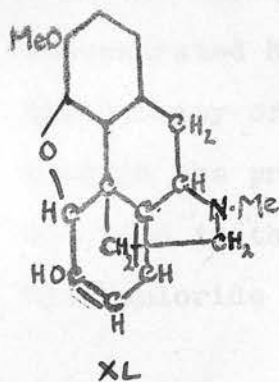
The stages in the production of thebenine may be represented in the following manner, where R represents  $-\text{CH}_2\text{CH}_2\text{NHMe}$ :



In the formation of the thebenine from codeinone (thebaine), there are only two possible explanations: either oxygen wanders, and this is very unusual in the case of a carbonyl group; or ring III revolves through  $180^\circ$  at some stage. It would appear therefore that the change must be represented by a scheme such as the following, and if this is correct the two schemes are related in that the group R migrates to that adjacent carbon atom which is most remote from the carbonyl group.



Schöpf and Borkowsky have criticised this scheme adversely, and have explained the formation of thebenine from codeinone by the addition of water (XLa) to the conjugated system produced in an enolic form of codeinone (XL), followed by the codeine- $\psi$ -codeine transformation (XLb), and migration of the ethanamine chain to C<sup>5</sup>. The stage (XLa) is the formula which must now be given to the hydroxycodine which is obtained by the reduction of the hydroxycodine<sup>73</sup> and it seemed interesting to test this theory by direct experiment (see Publication 10). It has been found that the hydroxycodine is quite unaffected by boiling hydrochloric acid (d 1.07, the strength used in the preparation of thebenine), and that prolonged heating with acetic anhydride yields no triacetyl thebenine but a mixture of two bases, one crystalline, the other amorphous. A consideration of these facts suggests that Schöpf's theory is improbable, although it is possible to advocate the sensitivity of the activated phases of a chain of reactions to evade this criticism.



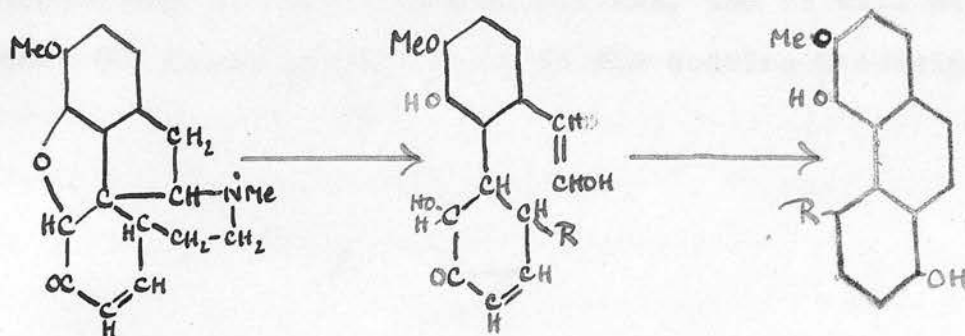
It is, of course, a matter of very great difficulty to investigate the nature of the intermediate stages in a reaction such as the formation of thebenine, particularly since the final product is formed in the course of a few seconds, but an experiment performed by the author does indeed allow some insight into the course of the change, and supports the theory of the rotation of ring III suggested above, whilst weighing heavily in the balance against the mechanism proposed by Schöpf. It appears from the work of Schöpf and Borkowsky on absorption spectra that thebaine and thebainone, when dissolved in concentrated hydrochloric acid, are closely related in structure, and that in consequence the carbon-to-carbon linkage of the ethanamine chain of thebaine under these conditions is attached to  $C^{14}$  (see p.52). That is, in concentrated hydrochloric acid migration of the chain of thebaine has occurred as proposed in the scheme of the formation of thebenine which involves ring-rotation, and in the opposite direction to that suggested by Schöpf (above). When the red solution obtained by dissolving thebaine in concentrated hydrochloric acid is diluted with water so that the density of the hydrochloric acid is 1.07 (the strength used in the preparation of thebenine), and the pale yellow solution is then boiled for three minutes and cooled, thebenine hydrochloride separates in an amount, which is identical with





it occurred, throw valuable light on the mechanism of thebenine formation.

In view of the results described above, it is clearly of interest to investigate the successive stages in the formation of thebenine using the alternative formula for thebaine (XXXIII) in which the ethanamine chain is already linked to C<sup>14</sup>, and here for the first time we receive a possible explanation of the remarkable difference in stability of codeinone and  $\psi$ -codeinone. The aromatic nature of ring III can only be ~~obt~~ained by enlargement from a five- to a six-membered ring, a change which involves migration or fission of the C<sup>13</sup> - C<sup>9</sup> bond, and since the appearance of a new carbon atom at C<sup>14</sup> would still inhibit the aromatic character of ring III, the only alternative part of attachment C<sup>5</sup>, is chosen; this result can only be made possible by revolution of ring III.

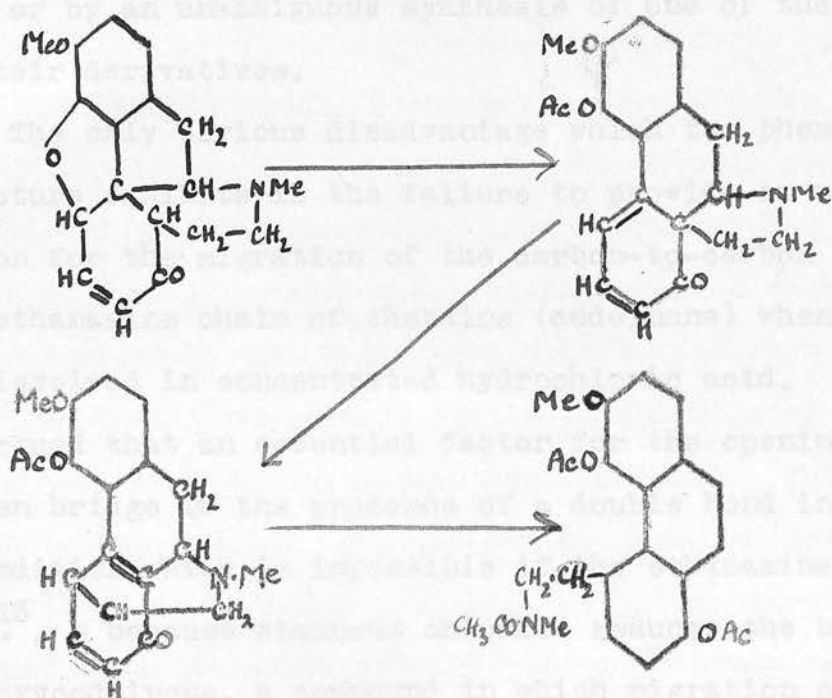



---

\* Codeinone yields thebenine in the course of a few moments when heated in boiling dilute hydrochloric acid, whereas the action of boiling acetic anhydride for several hours is required to produce triacetylthebenine from  $\psi$ -codeinone.

Reactions of this type, in which an aliphatic five-membered ring becomes enlarged to a benzenoid ring are by no means uncommon, and a recent interesting example in which such a change is postulated is the formation of chrysene by the <sup>74</sup>dehydrogenation of cholesterol.

On the other hand, when the formation of triacetylthebenine from  $\psi$ -codeinone is studied by means of this formula, it is difficult to see why any derivative of thebenine should be ~~formed~~<sup>formed</sup>, and why the reaction does not lead to the production of the isomeric 6-hydroxy-derivative by stages which are similar to the formation of thebenine from codeinone. Since this is certainly not the case, it is evident that the explanation of the  $\psi$ -codeinone-thebenine transformation by means of the hydrindane formula involves two migrations. First, C<sup>9</sup> wanders to C<sup>14</sup>, and then C<sup>13</sup> migrates to C<sup>5</sup>. The detailed scheme may be represented as follows, and it will be seen that the second migration is of the codeine- $\psi$ -codeine type.



It will have been observed during the course of the discussion of the effect of acids on thebaine that frequent comparison has been made between two alternative formulae, (p.28) and (XXXIII), for thebaine, and it is now necessary to consider which of these gives the more correct representation of the properties of the alkaloids. It may be stated at once that the available experimental evidence is in favour of that formula, (p.28), which retains the phenanthrene nucleus, but it must be realised that the ultimate decision between these possibilities will only be made possible by further experimental

work or by an unambiguous synthesis of one of the alkaloids or their derivatives.

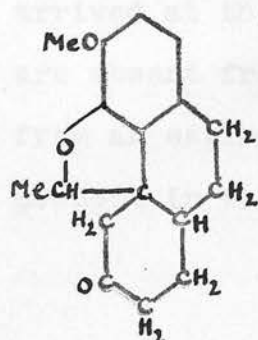
The only serious disadvantage which the phenanthrene structure exhibits is the failure to provide an adequate reason for the migration of the carbon-to-carbon linkage of the ethanamine chain of thebaine (codeinone) when the alkaloid is dissolved in concentrated hydrochloric acid. It cannot be argued that an essential factor for the opening of the oxygen bridge is the presence of a double bond in  $C^5 - C^{13}$ , - a condition which is impossible if the ethanamine chain rests on  $C^{13}$ , - because stannous chloride reduces the bridge of hydroxycodeinone, a compound in which migration of the chain to  $C^{14}$  is prevented by the hydroxyl group. Moreover, there can be no operation of a driving force, such as aromatic-ring formation, and the explanation of this important question must be shelved, although the fact must be accepted in the absence of further experimental criticism.

Turning to the alternative formula for the alkaloids (XXXIII), some of its advantages have been discussed in the preceeding pages, and the apparent discrepancy in structure between it and the phenanthrene derivatives of the series is in reality non-existent, when it is remembered that this group of compounds is formed in conditions in which isomerisation ( $C^9$  becomes attached to  $C^{14}$  instead of  $C^{13}$ ) is to be

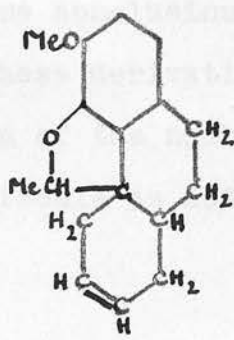


expected. There are however two disadvantages of this formula which cannot be overlooked. The first point where the formula breaks down is in accounting in a rational way for the isomerisation of  $\alpha$ - and  $\gamma$ -methylmorphimethines into  $\beta$ - and  $\delta$ -methylmorphimethines respectively. The second pair of compounds are best represented as arising from the first by the shift of a double-bond from  $C^7-C^8$  to  $C^8-C^{14}$  so that a conjugated system is formed with the unsaturated link of the phenanthrene bridge. This change cannot be represented by means of the formula (XXXIII) and further, it is clear that the  $\alpha$ - and  $\beta$ -series of the methines have the same carbon skeleton because  $\alpha$ - and  $\beta$ -methylmorphimethines yield the same tetrahydro-derivative<sup>75</sup> on reduction. Additional confirmation of this observation, so important in the present case, is obtained from the analogous behaviour of the  $\alpha$ - and  $\beta$ -dimethylmorphimethines.<sup>76</sup>

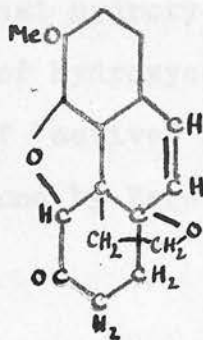
The second point which cannot be satisfactory<sup>il</sup> explained by the formula (XXXIII) is the representation of certain non-nitrogenous derivatives. Thus thebenone (XLII), the non-nitrogenous compound (XLIII) prepared by the exhaustive methylation of deoxytetrahydro- $\alpha$ -methylmorphimethine,<sup>77</sup> dihydrohydroxycodeone (XLIV), and tetrahydrohydroxythebaone<sup>78</sup> and its methyl ether<sup>79</sup> (XLV) are more suitably represented by means of the phenanthrene structure (p.28).



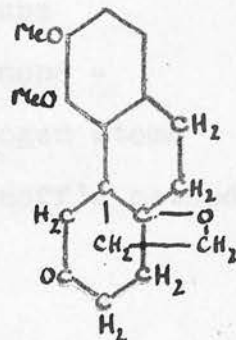
XLII



XLIII



XLIV



XLV

Each of these compounds contains an oxide ring which is of the conventional, stable, 5-membered type if the two-carbon chain is attached to C.<sup>13</sup>, and the particular interest in the present connection lies firstly in the formation of oxide rings in two directions (with oxygen at C.<sup>4</sup> and at C.<sup>14</sup>), and secondly in the fact that the oxide rings in the hydroxycodone series (see below for evidence of their existence) exhibit a stability which is not in harmony with the presence of a 4-membered oxide ring, whereas the attachment of the ethanamine chain to C.<sup>14</sup> would necessitate the presence of a ring of this type. The author has prepared dihydrohydroxycodone from dihydrohydroxycodone in the manner described by Freund and Speyer, and has found that it shows none of the general reactions characteristic of hydroxylic compounds (acetylation, benzylation, interaction

with phenyl isocyanate), and Schöpf and Borkowsky have arrived at the same conclusion - that hydroxy-groups are absent from these derivatives of hydroxycodoinone - from an estimation of the number of "active" hydrogen atoms present in the molecule as determined by Zerewitinoff's method.

## THE REDUCTION OF THEBAINE

---

Among the more interesting and remarkable researches in morphine chemistry must be counted the investigations into the reduction of thebaine under various conditions, which have been made from time to time by different workers. These researches have now arrived at such a stage that it is possible to make a comprehensive survey of the field.

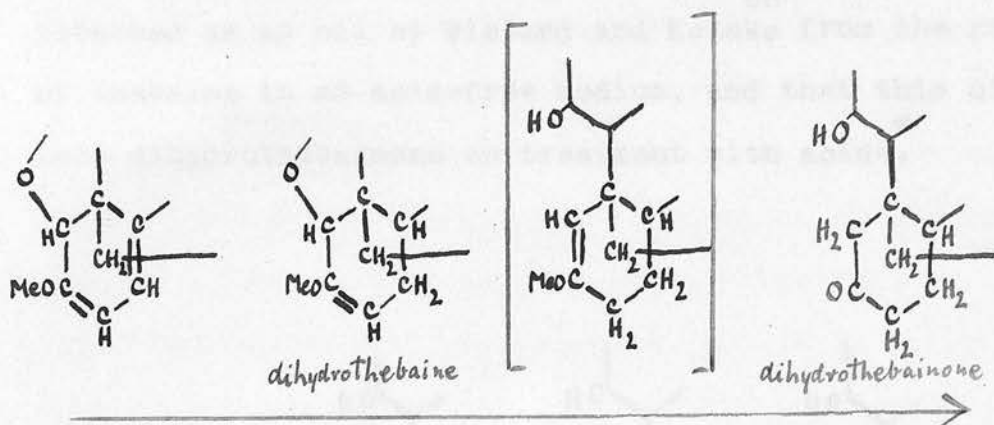
It has been shown earlier (p.33 ) that the oxygen bridge may react as the end of a conjugated system when there is a double bond at C<sup>6</sup>-C<sup>7</sup>, and in the light of this conception the structure assigned to thebaine virtually contains a conjugated system of three unsaturated linkages. The nature of the reactions which occur when thebaine is reduced may all be elucidated by the addition of hydrogen to various points in this system in accordance with Thiele's hypothesis. Schöpf has adopted a similar view in considering the reduction of thebaine but he has not extended this to include phenolic dihydrothebaine (see below).

A study of the literature of the subject leaves no doubt that in catalytic reduction the various modes of hydrogenation proceed concurrently, and lead to the formation of a mixture of products, some of which may not have suffered complete reduction under the conditions of the experiment.

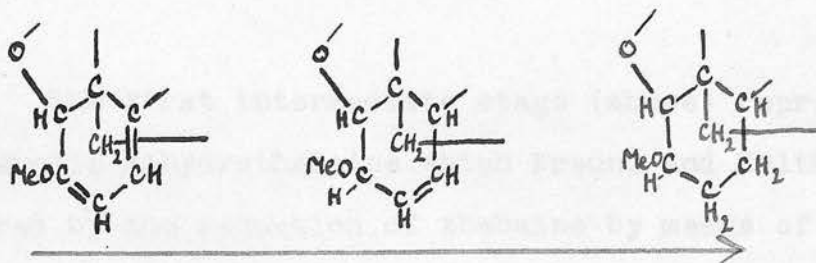
This is in accordance with many observations made by the author in the preparation of dihydrothebaine and dihydrothebainone for experimental purposes, where a mixture of these two bases with amorphous substances was always obtained in any catalytic reduction of thebaine (Publication 2, and unpublished observations), and Cahn and Schöpf and Winterhalder have reported similar results. Oldenburg's original observation that thebaine absorbed two molecules of hydrogen and yielded an amorphous base is probably a further example of such a mixture.

1:2 Addition at C<sup>8</sup> and C<sup>14</sup> occurs when the experimental conditions are mild, and the main product, dihydrothebaine, is not reduced further under these circumstances. Hydrolysis by boiling hydrochloric acid removes the aliphatic methoxyl group of this base, and dihydrocodeinone is formed. This hydrolysis, which is analogous to the formation of codeinone from thebaine, indicates that the "enolic" double bond of dihydrothebaine has remained intact. More energetic reduction of dihydrothebaine in acetic acid solution attacks the 1:4-positions of the residual conjugated system, the oxygen bridge is opened, and dihydrothebainone is formed by hydrolysis of the methoxyl group.





1:4 Addition at C<sup>6</sup> and C<sup>14</sup> leads to the production of the  
 80  
 non-phenolic tetrahydrothebaine, which does not undergo  
 hydrolysis in acid solution.

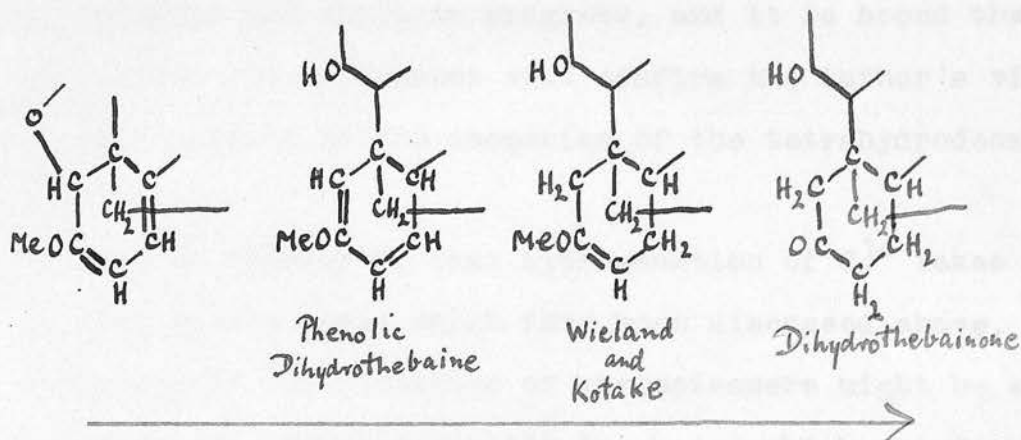


1:6 Addition at Oxygen and C<sup>14</sup>, followed by further reduction  
 at the ends of the system C<sup>5</sup> - C<sup>8</sup> and hydrolysis of the  
 85\*  
 methoxyl, yields dihydrothebainone. It is interesting to

\* Small quantities of dihydrothebainol, the secondary alcohol corresponding to dihydrothebainone, have been isolated by Skita and his co-workers from the catalytic reduction of thebaine in dilute acetic acid.



note that the second intermediate stage has actually been<sup>86</sup> obtained as an oil by Wieland and Kotake from the reduction of thebaine in an acid-free medium, and that this oil passes<sup>\*</sup> into dihydrothebainone on treatment with acids.



The first intermediate stage (above) represents the<sup>87</sup> phenolic dihydrothebaine which Freund and Holthoff prepared by the reduction of thebaine by means of sodium and alcohol, and in this reaction 1:6-addition proceeds to the exclusion of the other alternatives. The author has repeated the work of these investigators and is able to confirm their results. The product contains two methoxyl groups, one of which is hydrolysed by acid,

---

\* Their hypothesis that a cyclopropane ring is present is untenable.

and in this way an unstable amorphous ketone is formed.\*  
 A number of unsuccessful attempts were made to reduce this catalytically, and in other ways, with the intention of preparing dihydroepithebanone, since the author considers that in all probability the configuration at C<sup>14</sup> is the reverse of that which occurs in the codeine series. These experiments are still in progress, and it is hoped that their successful accomplishment will confirm the author's views on the question of the isomerism of the tetrahydrodeoxycodeines.

It is noteworthy that hydrogenation of C<sup>14</sup> takes place in each of the cases which have been discussed above, and consequently the formation of stereoisomers might be expected. Nevertheless, practically all the bases which are formed by the catalytic reduction of thebaine have the same configuration

---

\* Dihydrothebaine was prepared exactly as described by Freund and Holthoff, and the amorphous product, when quite dry, was crystallised twice from ethyl acetate. It formed colourless prisms, m.p. 153°, which dissolved in warm, dilute sodium hydroxide, and was precipitated unchanged by the addition of ammonium chloride to this solution. (Found in material dried at 100°: C, 72.8; H 7.5; OMe, 20.1. Calc. for C<sub>19</sub>H<sub>23</sub>O<sub>3</sub>N: C, 72.9; H 7.3; (OMe)<sub>2</sub>, 19.8%). The unsaturated character of the ketone formed by hydrolysis, and the position of the double-bond at C<sup>7</sup>-C<sup>8</sup>, are shown by the development of an orange yellow colour in concentrated sulphuric acid, by the absence of colour in concentrated hydrochloric acid, and by the formation of a deep yellow solution in sodium hydroxide. The methiodide crystallised in faintly yellow prisms, m.p. 154° (decomp.).

at C.<sup>14</sup>, - namely, that of codeine (see later, p. 81 ).

Dihydrothebaine, for example, is converted by hydrolysis of the methoxyl into dihydrocodeinone, which in its turn is formed from codeine by reduction of a double bond at C7 - C8, and the hydrogen at C.<sup>14</sup> plays no part in these reactions. Further, tetrahydrothebaine is identical with dihydromorphine dimethyl ether which Mannich obtained by O-methylation and catalytic reduction of codeine. The only exceptions in catalytic reductions which may have the reverse configuration at C.<sup>14</sup> are Schöpf's epidihydrothebainone (p. 46) and possibly the tetrahydrothebaine, m.p. 144°, prepared by Skita, Nord, Reichert, and Stukart, and the base which Freund, Speyer, and Guttmann isolated as a methiodide, m.p. 246°.

# THE DEOXY-COMPOUNDS AND SOME STEREOCHEMICAL RELATIONSHIPS

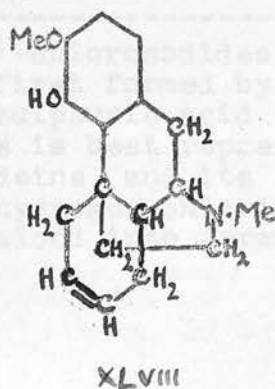
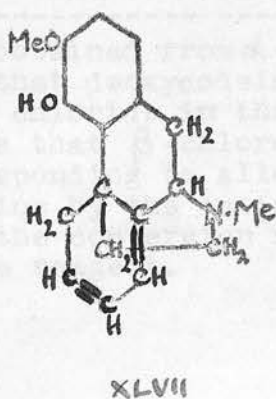
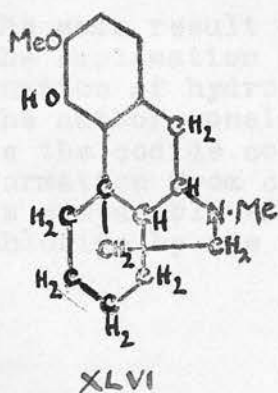
The term "deoxy" is applied to those compounds of the normal or pseudo-codeine series in which the oxygen of the alcoholic hydroxyl has been eliminated in the course of a reduction of the molecule. <sup>\*</sup> A considerable number of these substances have been prepared, as will be seen by reference to the accompanying scheme of morphine derivatives, but hitherto no attempt has been recorded to explain the mutual relationships of the members of this group of compounds.

When  $\alpha$ -chlorocodide (ex codeine) or  $\psi$ -chlorocodide (ex  $\psi$ -codeine) is reduced by means of zinc dust and absolute alcohol, the oxygen bridge is broken and the tertiary basic deoxycodine<sup>88</sup> is produced. The phenolic character of this substance is evident from the solubility in alkali of a freshly-precipitated specimen, and from the formation of an acetyl-derivative and a methylether methiodide. Further light is shed on the chemical constitution by the ease with which deoxycodinemethine methyl-ether or its methiodide yields dimethylmorphol (p. 5 ) on treatment with dilute hydrochloric acid or sodium hydroxide respectively. Clearly, the molecule of deoxycodine is in a suitable state of oxidation (compare p. 36 ) to yield an aromatic nitrogen-free derivative, and this condition is only made possible by the presence of two double bonds in ring III. This view is

---

\* The statement frequently made that the -CHOH- group of the alcohol is reduced to a methylene-group, -CH<sub>2</sub>-, is erroneous.

confirmed by a study of the reduction of deoxycodine, since four atoms of hydrogen may be taken up either in one or in two stages according to the reagents employed. The position of one of these unsaturated linkages may be inferred from the facts that the reduction of deoxycodine by sodium and alcohol yields the fully-reduced  $\alpha$ -tetrahydrodeoxycodine (XLVI), whilst the reduction of deoxycodine hydrochloride by palladium and hydrogen produces the isomeric  $\beta$ -tetrahydrodeoxycodine (XLVII). Both these substances are phenolic tertiary bases, and a consideration of the other methods by which they may be prepared precludes any other explanation of the isomerism than that of stereoisomerism at C<sup>14</sup>. If this view be accepted, one of the double bonds of deoxycodine must rest at C<sup>14</sup>, and the formation from  $\psi$ -chlorocodide suggests C<sup>6</sup> - C<sup>7</sup> as the probable position of the second unsaturation. Deoxycodine therefore receives the formula (XLVIII), and it seems probable that during its formation the normal codeine structure isomerises to the  $\psi$ -codeine type, and that the double bond in C<sup>8</sup> - C<sup>14</sup> is produced by elimination of hydrogen chloride.





\*

Electrolytic reduction of deoxycodine yields dihydro-deoxycodine, m.p. 117° (XLVIII), not by reduction at the ends of the conjugated system, but by reduction of the double bond between C<sup>8</sup> and C<sup>14</sup>, as is shown by the production of the same base when chlorodihydrocodide (ex dihydrocodine and phosphorous pentachloride) is reduced under identical conditions. In this case the double bond in position C<sup>6</sup> - C<sup>7</sup> is due to loss of hydrogen chloride in the sulphuric acid employed. Catalytic reduction of dihydrodeoxycodine, m.p. 117°, yields  $\alpha$ -tetrahydro-deoxycodine or the steps may be reversed, since chlorodihydrocodide when reduced catalytically gives a non-phenolic, amorphous dihydrodeoxycodine (XLIX), which in its turn is reduced electrolytically to  $\alpha$ -tetrahydrodeoxycodine. It is clear that this base and the two dihydrodeoxycodines from which it is formed must have the same configuration as codeine (see later), since all may be obtained from chlorodihydrocodide.

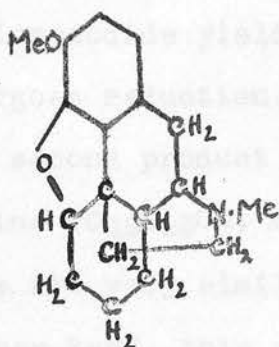
Turning now to the catalytic reduction of deoxycodine, the addition of four hydrogen atoms saturates the molecule and the  $\beta$ -tetrahydrodeoxycodine which results must have the

---

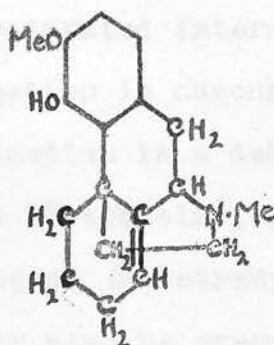
\* The same result is obtained from  $\alpha$ - or  $\beta$ -chlorocodides, and the explanation is that deoxycodine is first formed by elimination of hydrogen chloride in the 20% sulphuric acid employed. The author considers that  $\beta$ -chlorocodide is best represented as the codide corresponding to allo- $\gamma$ -codeine, and its formation from codeine by the action of hydrogen chloride is comparable with the conversion of linalool into geranyl chloride by the same reagent.



reverse configuration at C<sup>14</sup>. The yield here is quantitative, and the suggestion is now made that catalytic reduction of a conjugated system containing a double bond in the position C<sup>8</sup> - C<sup>14</sup> (excluding reductions of thebaine) introduces the hydrogen on C<sup>14</sup> in the opposite sense stereochemically to that in which it is placed in codeine. Confirmation of this idea may be obtained from two sources: Firstly, the electrolytic reduction<sup>91</sup> of bromocodeinone produces a second phenolic dihydrodeoxycodeine,<sup>\*</sup> m.p. 140°, which is probably represented by (L), and catalytic reduction of this base yields  $\beta$ -tetrahydrodeoxycodeine in quantitative yield.<sup>91</sup> Secondly, the methine of dihydrohydroxythebainone



XLIX



L

---

\* It is not entirely excluded that a Walden inversion at C<sup>14</sup> takes place during the electrolytic reduction, in which case this dihydrodeoxycodeine would retain the double bond of bromocodeinone at C<sup>7</sup> - C<sup>8</sup>, but this seems unlikely in view of the reduction of bromocodeinone to codeinone by means of iron and sulphuric acid.

readily loses water in hydrochloric acid solution, whereas the parent base is stable, and this difference can only be explained by the loss of water between C<sup>14</sup> and C<sup>8</sup>. Catalytic reduction of the base thus formed leads to the production of a dihydrothebainonemethine which is isomeric (presumably about C<sup>14</sup>) with that prepared from dihydrothebainone.<sup>80</sup>

A second non-phenolic dihydrodeoxycodine (dehydroxydihydrocodeine), m.p. 107°, has been obtained by Mannich and Löwenheim<sup>92</sup> by the catalytic reduction of  $\beta$ -chlorocodide, and the author suggests tentatively that it is a stereoisomeride (at C<sup>14</sup>) of the amorphous dihydrodeoxycodine obtained from chlorodihydrocodide, and that in its formation hydrogen chloride is eliminated from  $\beta$ -chlorocodide yielding an unsaturated intermediate which then undergoes reduction. The question is obscure, however, because a second product of the reduction is a dehydroxytetrahydrocodeine (C<sub>18</sub>H<sub>25</sub>OH, Mannich and Löwenheim), of which the properties are very similar to those of  $\beta$ -tetrahydrodeoxycodine. On the other hand, this compound may also be prepared by the reduction of dihydrocodeinone by Clemmensen's method, which<sup>92</sup> suggests the codeine configuration at C<sup>14</sup>, but the substance is clearly different from Speyer and Siebert's deoxydehydrothebaine<sup>93</sup> with which it should be identical if the empirical formula assigned by Mannich and Löwenheim is correct.

Finally, the actual spatial relationships in the molecules must be considered. Tetrahedral models of the three alkaloids

may be built up in a condition free from strain, and four points are immediately revealed by a study of these structures. (i) The bonds attaching the carbon and the nitrogen of the ethanamine chain must lie on the same side of ring II; (ii) the chain will lie "above" the general plane of the molecule; (iii) the hydrogen at C<sup>5</sup> is probably directed in the same "upward" direction as the ethanamine chain, since this arrangement produces a less strained oxygen bridge; (iv) no conclusion can be drawn regarding the actual configuration of the hydroxyl group in the isomeric codeines.

Turning to those compounds which are produced by a change in C<sup>14</sup>, water, bromine, and hydrogen peroxide react with the conjugated system of thebaine to form compounds which have the same configuration at C<sup>14</sup>, since bromocodeinone and hydroxycodeinone yield the same hydroxycodeinone oxime and bromocodeinone may be reduced to codeinone, which may be further reduced to codeine. The true configuration of the hydrogen in codeine is determined by the formation of cyclic ethers (p. 68) in the hydroxycodeinone series, a condition which is only possible if the hydroxyl-group lies on the same side of the molecule plane as the vinyl group. The hydrogen at C<sup>14</sup> is therefore in the cis-position to the ethanamine chain in codeine (morphine), in the same position in  $\alpha$ -tetrahydrodeoxycodeine, and in the trans-position in  $\beta$ -tetrahydrodeoxycodeine.

# REFERENCES

1. Monat. für Chemie 1883. 4. 700
2. Ber. 1882. 15. 1481, 2179.
3. Ber. 1882. 15. 1487.
4. Ann. 1883. 222. 203.
5. Fischer and Vongerichten, Ber. 1886. 19. 792.  
Knorr, Ber. 1889. 22. 181. 1113; 1894. 27. 1144.
6. Freund and Göbel, Ber. 1895. 28. 941.  
Knorr, Ber. 1904. 37. 3499.
7. Knorr, Ber. 1903. 36. 3074; 1904. 37. 3501.
8. Journ. Pharm. Chim. 1881. (5). 4. 23.
9. Pschorr, Seydel, and Stöhrer, Ber. 1902. 35. 4400.  
Vongerichten, Ber. 1902. 35. 4410.
10. Trans. 1918. 113. 218.
11. Ber. 1900. 33. 1810.
12. Vongerichten, Ber. 1898. 31. 51; 1897. 30. 2439.  
Vongerichten, and Dittmer, Ber. 1906. 39. 1718.
13. Pschorr, Zeidler, Dickhauser, Treidel, and Koch.,  
Ann. 1912. 391. 40.
14. Ach. and Knorr, Ber. 1903. 36. 3067.
15. Ach. and Knorr. loc.cit.  
Knorr and Hörlein, Ber. 1907. 40. 2042.  
Pschorr and Einbeck, Ber. 1907. 40. 1980.
16. Knorr and Schneider, Ber. 1906. 39. 1414.  
Pschorr, Vogtherr, Kulitz, and Roth, Ber. 1906. 39. 3130.
17. Pschorr, Vogtherr, Kulitz, and Roth. loc.cit.
18. M. 1922. 43. 255.

19. Knorr. Ber. 1889. 22. 181. 1113.  
Vongerichten. Ber. 1897. 30. 2439.  
Freund, Ber. 1897. 30. 1357.
20. Freund, Ber. 1897. 30. 1362.
21. Knorr, Ber. 1904. 37. 3494. 3499.
22. Knorr, Ber. 1904. 37. 3501; 1903. 36. 3074; 1905. 38. 3171.  
Pschorr, Seidel, and Stöhrer, Ber. 1902. 35. 4400.  
Vongerichten. Ber. 1902. 35. 4410.  
Knorr and Hörlein, Ber. 1907. 40. 2035, 2039, 3350.  
Pschorr and Busch. Ber. 1907. 40. 2001.
23. Knorr. Ber. 1903. 36. 3074; 1904. 37. 3499.  
Knorr and Hörlein. Ber. 1907. 40. 2032, 3341.  
Pschorr and Busch, loc.cit.
24. Knorr and Hörlein. Ber. 1907. 40. 376, 2032, 3352.  
Knorr and Waentig. Ber. 1907. 40. 3860.
25. Stedman. J. 1924. 125. 1373.  
Stedman and Barger. ibid. 1925. 127. 247.
26. Freund and Speyer. J. pr. Chem., 1916, 94. 135.  
Speyer, Selig, and Heil. Ann. 1922. 430. 1.
27. Freund. Ber. 1906. 39. 844.
28. Speyer and Sarre. Ber. 1924. 57. 1404.
29. Schöpf. Ann. 1927. 452. 211.
30. Ann. 1922. 430. 1.
31. Speyer and Sarre. Ber. 1924. 57. 1409.
32. Ann. 1925. 444. 69.
33. Borsche and Frank. Ber. 1924. 57. 1373.
34. Ruzicka. Helv. Chim. Acta. 1926. 9. 101
35. Loc.cit.
36. Skita and Frank. Ber. 1911. 44. 2865.
37. Cahn and Robinson. J. 1926. 908.



38. J. 1926. 903.
39. Anderson. Ann. 1851. 77. 356.  
Armstrong. Ann. 1871. 159. 391.  
Grimaux, Compt. Rend. 1881. 92. 1140. 1228.  
Dott. Pharm. J. Trans. 1882. 12. iii. 1009.  
Merck. Arch. Pharm. 1891. 229. 161.  
Göhlich. Arch. Pharm. 1893. 231. 235.  
Schryver and Lees. Trans. 1900. 77. 1024; 1901. 79. 563.  
Lees and Tutin. Proc. 1906. 22. 253.  
Lees. Proc. 1907. 23. 200.  
Knorr and Hörlein. Ber. 1906. 39. 4409  
1907. 40. 376. 2032.3341.4889.  
1908. 41. 969.  
Knorr and Roth. Ber. 1907. 40. 3355.  
Ach and Steinbock. Ber. 1907. 40. 4281.  
Oppé. Ber. 1908. 41. 975.  
Knorr, Butler, and Hörlein. Ann. 1909. 368. 305.
40. Ach and Knorr. Ber. 1903. 36. 3070.  
Knorr and Hörlein. Ber. 1907. 40. 4883.
41. Knorr. Ber. 1903. 36. 3074.
42. Knorr. Ber. 1904. 37. 3501.
43. Pschorr, Seydel, and Stöhrer. Ber. 1902. 35. 4400.  
Vongerichten. Ber. 1902. 35. 4410.
44. Knorr and Hörlein. Ber. 1907. 40. 2035.  
Knorr, Hörlein and Grimme. Ber. 1907. 40. 3844.  
Lees. Trans. 1907. 91. 1408.
45. Knorr and Hörlein. Ber. 1907. 40. 2039. 3350.
46. Ber. 1907. 40. 2001.
47. Fischer and Vongerichten. Ber. 1886. 19. 792.  
Knorr. Ber. 1889. 22. 1113; ibid. 1904. 37. 3494.
48. Ber. 1911. 44. 2633.
49. Ber. 1907. 40. 2827. 4146.
50. Pschorr. Ber. 1912. 45. 2212.
51. Pschorr, Seydel, and Stöhrer; Pschorr and Busch; loc.cit.

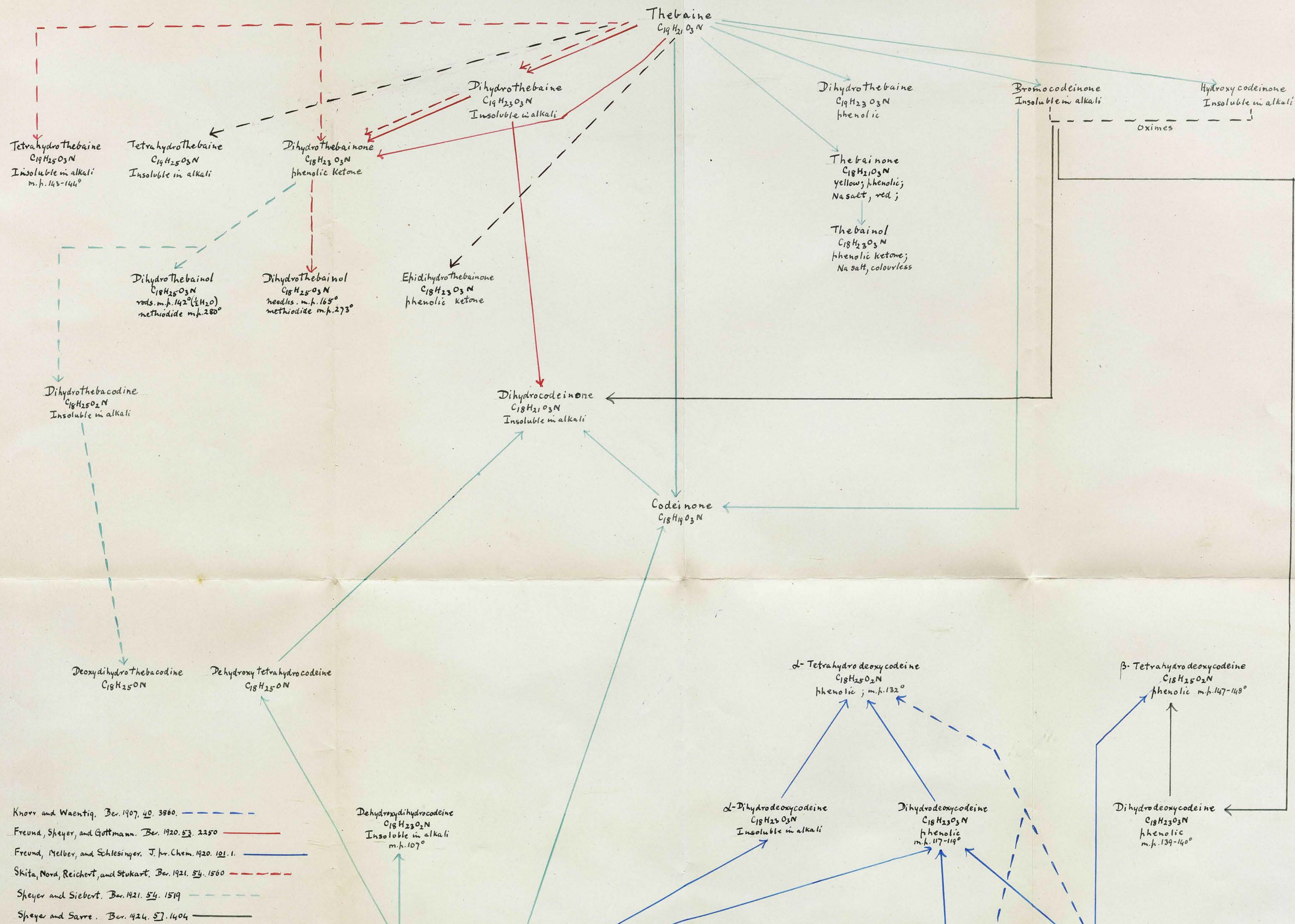


52. Speyer and Wieters. Ber. 1921. 54. 2647.  
Speyer and Krauss. Ann. 1923. 432. 233.  
Skita and Frank. Ber. 1911. 44. 2865.  
Wieland and Koralek. Ann. 1923. 433. 267.  
Speyer and Koulen. Ann. 1924. 438. 34.
53. Grimaux. Compt. Rend. 1881. 93. 591.  
Hesse. Ann. 1884. 222. 203.  
Vongerichten. Ber. 1899. 32. 1047. 2379.  
Knorr. Ber. 1894. 27. 1144.  
Schryver and Lees. Trans. 1901. 79. 577.  
Knorr and Smiles. Ber. 1902. 35. 3009.  
Knorr and Hawthorne. Ber. 1902. 35. 3010.  
Pschorr, Roth, and Tannhäuser. Ber. 1906. 39. 19.  
Knorr and Hörlein. Ber. 1906. 39. 4412.  
Knorr. Hörlein, and Grimme. Ber. 1907. 40. 3844.
54. Knorr. Ber. 1889. 22. 181. 1113; 1894. 27. 1144.  
Fischer and Vongerichten loc.cit.  
Knorr and Pschorr. loc.cit.  
Vongerichten. Ber. 1897. 30. 2439.
55. Freund. Ber. 1897. 30. 1357.  
Knorr. Ber. 1903. 36. 3074.
56. Knorr. Ber. 1894. 27. 1147; 1904. 37. 3495.
57. Knorr. Ber. 1904. 37. 3494. 3499. 3501.  
Knorr and Hörlein. Ber. 1907. 40. 2039. 3350.
58. Freund. 1897. 30. 1357.
59. Vongerichten and Schrötter. Ber. 1882. 15. 1487.  
Hesse. Ann. 1883. 72. 203.  
Vongerichten. Ber. 1896. 29. 65; 1898. 31. 51. 3198.  
1899. 32. 1521; 1900. 33. 352. 1810.  
1901. 34. 2722.  
Schryrer and Lees. Trans. 1901. 79. 578.  
Knorr, and Roth. Ber. 1911. 44. 2754.
60. Ber. 1905. 38. 3160.
61. Ibid. 3171.
62. Ber. 1920. 53. 2250.
63. Ber. 1921. 54. 1560.

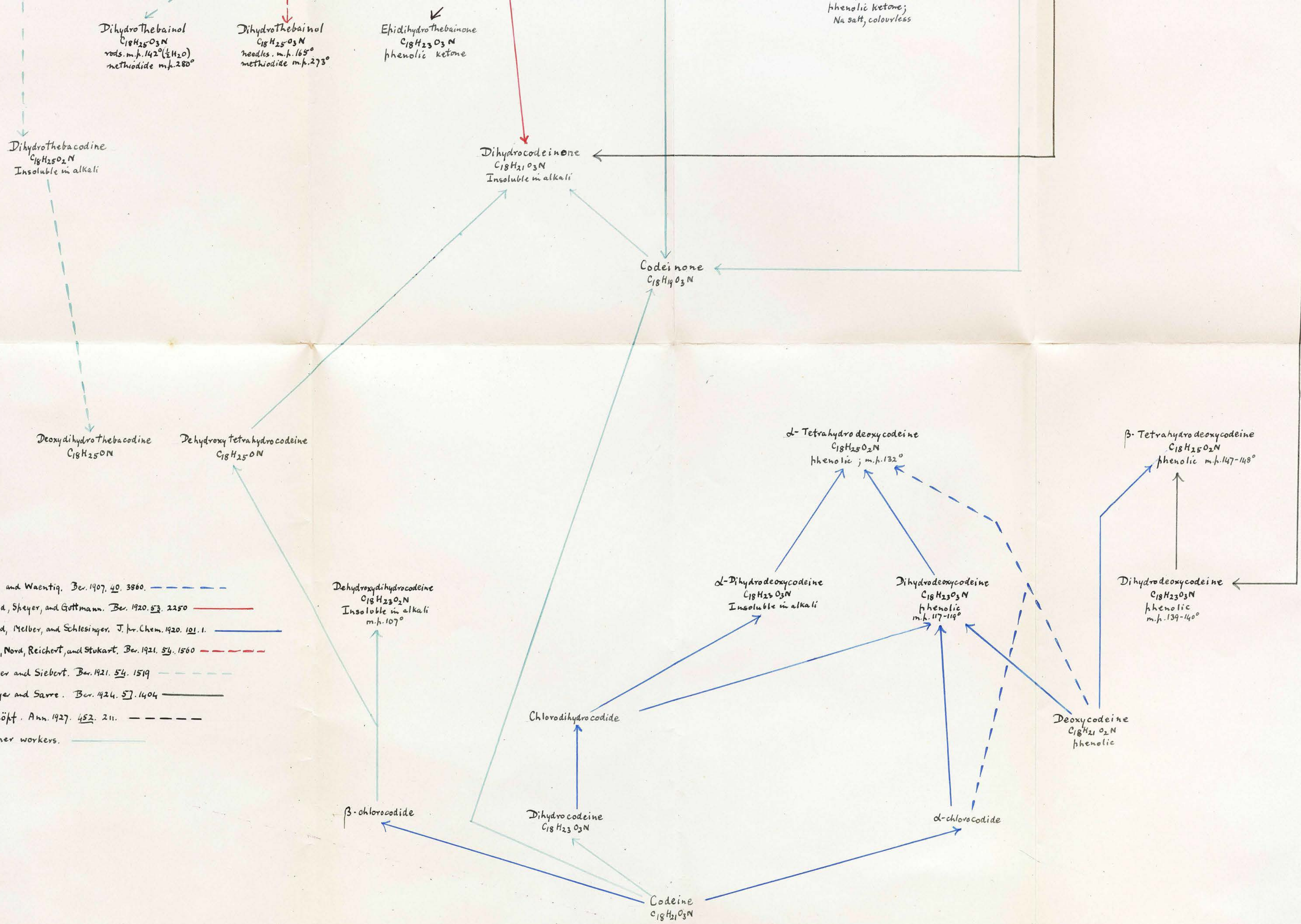
64. Ann. 1927. 458. 148.
65. Howard. Ber. 1884. 17. 527.  
Freund and Holthorff. Ber. 1899. 32. 168.  
Knorr. Ber. 1903. 36. 3074.  
Freund. Ber. 1899. 32. 173.  
Knorr and Pschorr. Ber. 1905. 38. 3153.  
Pschorr and Halle. Ber. 1907. 40. 2004.  
Pschorr and Rettberg. Ann. 1910. 373. 51.  
Pschorr and Knöffler. Ann. 1911. 382. 50.  
Klee. Arch. Pharm. 1914. 252. 211.
66. Matthieson and Wright. Ann. 1870, Suppl. 7. 172.  
Meyer. Ber. 1871. 4. 121.  
Liebert. Jahresbericht Fortschr. Chem., 1872. 755.  
Oberlin. J. Pharm. Chim. 1876. (4) 21. 89.  
Pschorr, Jaeckel and Fecht. Ber. 1902. 35. 4377.  
Pschorr and Karo. Ber. 1906. 39. 3124.  
Pschorr. Ber. 1907. 40. 1984; 1998; 2001.
67. Knorr and Roth. Ber. 1907. 40. 3356.  
Knorr and Rabe. Ber. 1908. 41. 3050.  
Pschorr, Jaeckel and Fecht. Ber. 1902. 35. 4387.
68. Ann., 1927. 458. 148.
69. Freund. Ber. 1897. 30. 1357; 1899. 32. 168.  
Knorr. Ber. 1903. 36. 3074.
70. Knorr and Hörlein. Ber. 1907. 40. 2037.
71. Ber. 1904. 37. 2780; 1907. 40. 2001.  
Ann. 1910. 373. 51. 75.
72. Loc.cit.
73. Freund and Speyer. J. pr. Chem. 1916. 94. 135.  
Speyer, Selig and Heil. Ann. 1922. 430. 1; Publication 3.
74. Diels and Gadke. Ber. 1927. 60. 140.
75. Braun and Cahn. Ann. 1927. 451. 57.
76. Faltis and Suppan. Chem. Zent. 1924. i. 918.
77. Wieland and Kotake. Ann. 1925. 444. 69.

78. Speyer and Koulen. Ann. 1924. 438. 34.  
Cahn. J. 1926. 2562.
79. Freund and Speyer. J. pr. Chem. 1916. 94. 135.  
Schöpf and Borkowsky. Ann. 1927. 452. 211.
80. Ann. 1927. 452. 211.
81. J. 1926. 2568.
82. Ann. 1927. 452. 232.
83. Ber. 1911. 44. 1829.
84. Freund, Speyer and Guttman. Ber. 1920. 53. 2250;  
Publication 2.
85. Skita, Nord, Reichert and Stukart. Ber. 1921. 54. 1560.
86. Ber. 1925. 58. 2009.
87. Ber. 1899. 32. 168.
88. Knorr and Hörlein. Ber. 1907. 40. 376, 2032, 3352, 4883.  
Knorr and Waentig. Ber. 1907. 40. 3860.  
Gölich. Arch. Pharm. 1893. 231. 235.  
Lees. T. 1907. 91. 1408.
89. Knorr and Waentig. Ber. 1907. 40. 3860.
90. Freund, Melber and Schlesinger. J. pr. Chem. 1920. 101. 1.
91. Speyer and Sarre. Ber. 1924. 57. 1404.
92. Arch. Pharm. 1920. 258. 295.
93. Speyer and Siebert. Ber. 1921. 54. 1519.









Knorr and Waentig. Ber. 1907. 40. 3860. ————

Freund, Speyer, and Gottmann. Ber. 1920. 53. 2250 ————

Freund, Melber, and Schlesinger. J. pr. Chem. 1920. 101. 1. ————

Skita, Nord, Reichert, and Stukart. Ber. 1921. 54. 1560 ————

Speyer and Siebert. Ber. 1921. 54. 1519 ————

Speyer and Sarre. Ber. 1924. 57. 1404 ————

Schöpf. Ann. 1927. 452. 211. ————

Other workers. ————



PART II.

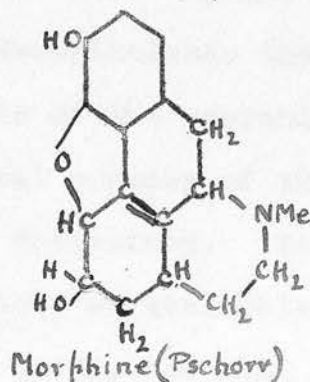
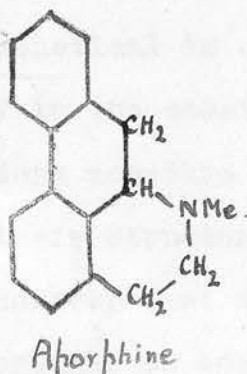
THE CONSTITUTION OF THE APORPHINE ALKALOIDS.





# INTRODUCTION

It is a natural sequence of a study of the morphine<sup>\*</sup> alkaloids to pass to a consideration of the aporphine series, a large group of bases which contain fundamentally the phenanthrene and isoquinoline ring-systems fused together. Many of the members of this series occur in Nature, a few on the other hand are produced by the interaction of the three morphine alkaloids with concentrated hydrochloric acid, and the interest of chemists has in the past been directed to, and is still focussed on a study of their constitution for two main reasons. Firstly, a study of the constitution of those which were obtained for the morphine alkaloids was clearly of the greatest importance in aiming at a knowledge of the structure of morphine, and in this connection the remarkable researches of Pschorr deserve especial mention, since they led him to propound his well-known formula.




---

\* The series is named after the simplest member, aporphine, which was prepared synthetically by Gadamer.

Secondly, the naturally occurring aporphine bases are so widely distributed in different botanical families that the complete comprehension of their constitution and relationships cannot fail to afford considerable insight into the mode of formation and *raison d'être* of alkaloids in plants.

It is impossible to discuss in detail the analytical experiments in this field which are the outcome of the patient investigations of Pschorr, and more especially, of Gadamer, since steady progress has been hindered by wrong assumptions, - as in the earlier work in the corytuberine series -, or has been accelerated by brilliant conclusions based on scanty experimental evidence. Moreover, such a discussion would be outside the province of this thesis because the work in which the author has been engaged has been purely synthetical in character. Nevertheless, the close similarity in the chemical properties of the aporphine alkaloids renders possible a brief general summary of the processes by which their structures have been determined. It should be realised however that the whole battery of available reactions has been brought to bear in but few cases, and that frequently

it has been possible to determine the constitution of one member by a comparison of some of its properties with those of another. In this connection, apomorphine has usually been regarded as the foundation stone of the aporphine group, and the author proposes to describe most of the general reactions with reference to this base.

## THE REACTIONS OF THE APORPHINES

---

### (1) Exhaustive Methylation.

Probably few series of reactions have had such far-reaching results as the sequence of degradation known as "exhaustive methylation". (Hoffmann). The methohydroxide of the fully-methylated aporphine base is heated, or, more generally a solution of the methiodide in sodium hydroxide is boiled. The elements of water are eliminated from the molecule, and in most cases the methine which is produced is an optically inactive phenanthrene in which the nitrogen atom has broken away from C<sup>9</sup>. In a few instances, however, the alternative active 9-dimethylamino-8-vinyl-9:10-dihydrophenanthrene is also formed, and Gadamer in reviewing the question has shown that these reactions proceed in both directions simultaneously, and that the predominant course is dependant on the concentration of the solutions employed.

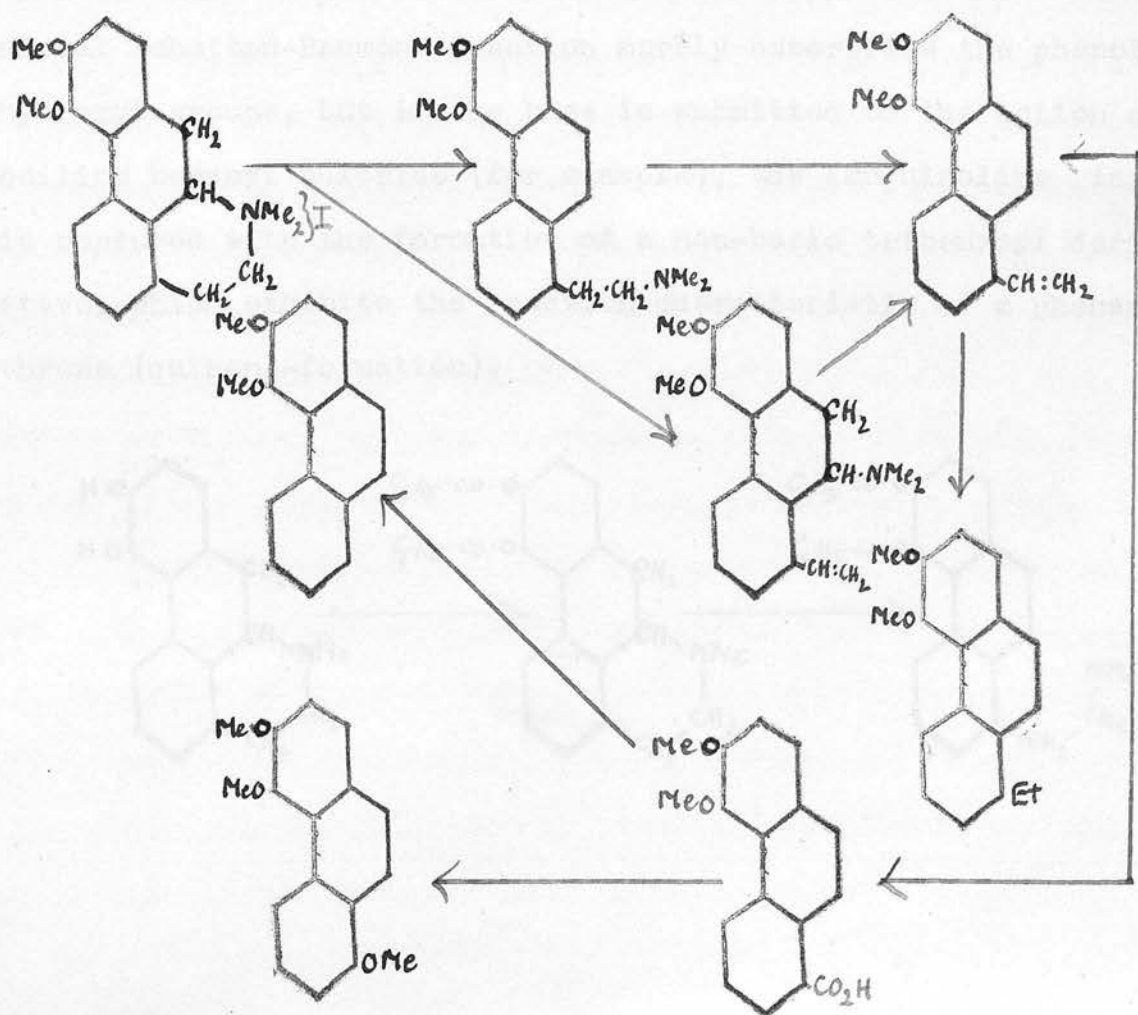
The inactive methine methiodide, when submitted to treatment similar to that described above yields a vinyl phenanthrene, which is also formed by the spontaneous elimination of trimethylamine and hydriodic acid from the methiodide of the active methine.

The nature of the vinyl phenanthrene is then determined in one of three ways. It may be distilled with zinc dust,

---

\* Notably in the case of isothebaine.

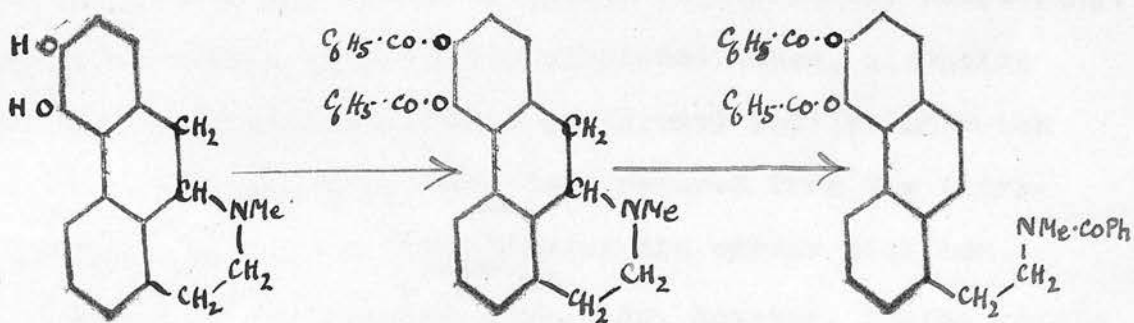
when the oxygen atoms are reduced, and the vinyl-group appears as the ethyl-group in an ethylphenanthrene. This method is <sup>2</sup> unsatisfactory, however, since Pschorr and Karo have observed the formation of two isomeric ethylphenanthrenes in the reaction. More certain results are obtained, therefore by reducing the vinyl-group catalytically, or by oxidising it to a carboxyl-group, which is either removed by heating or converted in its turn into methoxyl. These ultimate products of degradation are then synthesised in order that the specimens may be compared directly, and the steps of this synthesis have already been outlined (p. 7 ).





In the glaucine and corytuberine series the synthesis of the substituted phenanthrene derivatives was not effected by Gadamer. Nevertheless, his synthesis of glaucine itself<sup>3</sup> obviated the need for such experiments in that instance, and the synthesis of the ethers of the corytuberine group of alkaloids with which the author has been engaged have proved conclusively the position of the oxygen atoms in these compounds.

(2) Acylation has produced results which are so characteristic of the group that their appearance in the investigation of an alkaloid may be used to designate it an aporphine base. The normal Schotten-Baumann reaction merely esterifies the phenolic hydroxyl groups, but if the base is submitted to the action of boiling benzoyl chloride (for example), the isoquinoline ring is ruptured with the formation of a non-basic tribenzoyl derivative, which exhibits the reaction characteristic of a phenanthrene (quinone-formation).



Gadamer and Knoch have observed that a similar ring-fission of these bases may be brought about at room temperature by means of chloroformic ester, a reagent which may thus be used to characterise an isoquinoline base, since it is without action **on** the piperidine, pyrrolidine, and tetrahydroquinoline systems.

### (3) Oxidation reactions.

Destructive oxidation has played but a small part in the chemistry of the aporphine bases, and two examples will illustrate the nature of the results obtained. Gorter isolated 1:2-dimethoxybenzene-3:4:5-tricarboxylic acid from the oxidation of laurotetanine by permanganate, and thus deduced the presence of a catechol nucleus in the isoquinoline portion of the molecule. Warnat assigned a phenanthrene structure to boldine since he prepared from it 1:2:3:4 benzene tetracarboxylic acid by oxidation with nitric acid.

Milder oxidations have, however, proved remarkably fruitful, and in particular the action of iodine is especially noteworthy. In the case of many of the fully alkylated bases, alcoholic iodine forms dehydro-compounds - quaternary iodides in which two or four hydrogen atoms have been removed from the tetrahydropyridine ring without destroying the carbon skeleton. With a number of the phenolic alkaloids, however, iodine reacts in a peculiarly specific manner: apomorphine, bulbocapnine, and isocorydine for example, yield a green quinhydrone compound

(Pellagri reaction) indicating that the para-position to a hydroxyl group (on C<sup>4</sup>) is vacant: corytuberine and corydine on the other hand do not give the Pellagri reaction, and Gadamer has therefore assumed that corydine bears a hydroxyl group on C<sup>3</sup>. The case of corytuberine is more difficult. Its susceptibility to atmospheric oxidation when in alkaline solution undoubtedly proves the presence of two hydroxyls in the ortho-position with respect to each other, and the non-identity of its dimethyl ether with glaucine (constitution proved by synthesis) led Gadamer to allocate the hydroxyls to C<sup>3</sup> and C<sup>4</sup>, and to assume that the hydroxyl which takes part in the Pellagri reaction is occupied in the formation of a phenol-betaine, which is not found in the similarly constituted, but less basic, apomorphine.

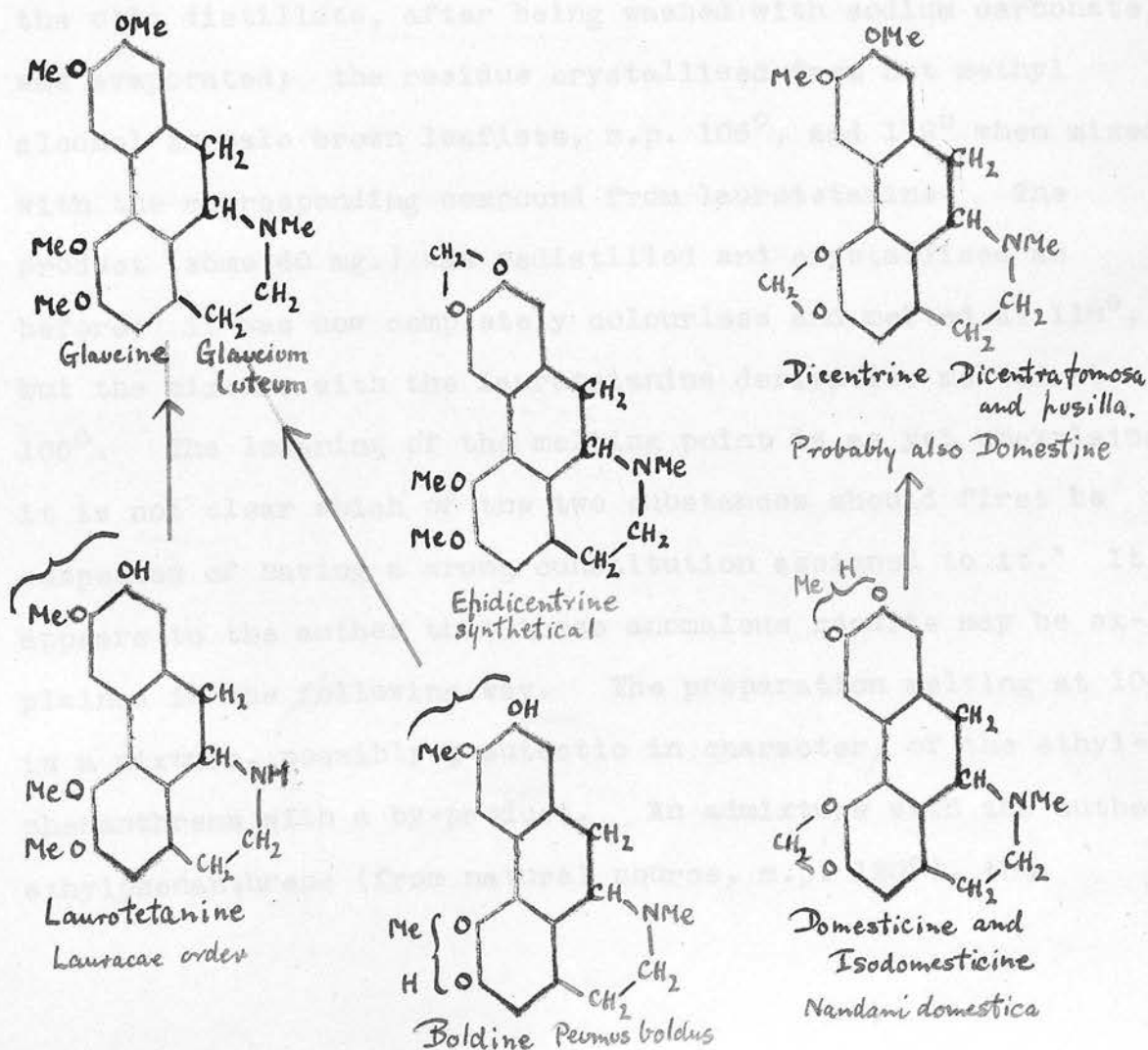
(4) Finally, considerable advantage has been taken of the observation of physiological action and the comparison of complex colour reactions, such as those produced by sulphuric acid or by Erdmann's, Fröhde's, or Mandelin's reagents, in determining the position occupied by hydroxyl groups or their ethers.

# CLASSIFICATION OF THE APORPHINE BASES

---

The bases of the aporphine series fall naturally into four groups, distinguished mutually as much by the position of the oxygen atoms as by their distribution in nature or mode of formation. In the schemes which follow, arrows indicate that methylation converts one member of a group into another.

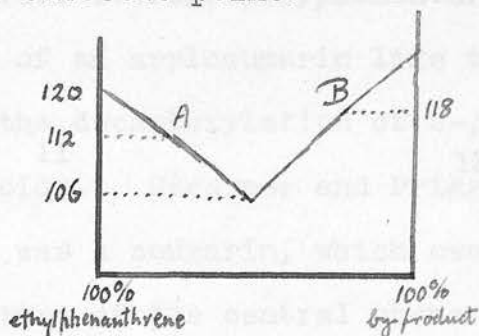
## (A) The Glaucine Group. All dextro-rotatory.



The recent publications<sup>8</sup> of Barger and Silberschmidt and of Späth and Strauhal<sup>9</sup> have proved that laurotetanine is really a partially demethylated glaucine, and cannot therefore be represented as a derivative of 2:3:6:7 tetramethoxyaporphine.<sup>5</sup> In Barger and Silberschmidt's paper (p. 2927), some difficulty has been experienced in the direct comparison of synthetical and natural specimens of 2:3:5:6 tetra-methoxy-8-ethylphenanthrene. Thus "the crude acid" (2:3:5:6-tetramethoxy-8-ethylphenanthrene-9-carboxylic acid) "was decarboxylated by heating 0.2 g. in a bath at 230 - 250°/9 mm. An ethereal solution of the oily distillate, after being washed with sodium carbonate, was evaporated; the residue crystallised from hot methyl alcohol in pale brown leaflets, m.p. 106°, and 112° when mixed with the corresponding compound from laurotetanine. The product (some 40 mg.) was redistilled and crystallised as before; it was now completely colourless and melted at 118°, but the mixture with the laurotetanine derivative melted at 106°. The lowering of the melting point is as yet unexplained; it is not clear which of the two substances should first be suspected of having a wrong constitution assigned to it." It appears to the author that these anomalous results may be explained in the following way. The preparation melting at 106° is a mixture, possibly a eutectic in character, of the ethylphenanthrene with a by-product. An admixture with the authentic ethylphenanthrene (from natural source, m.p. 120°), the

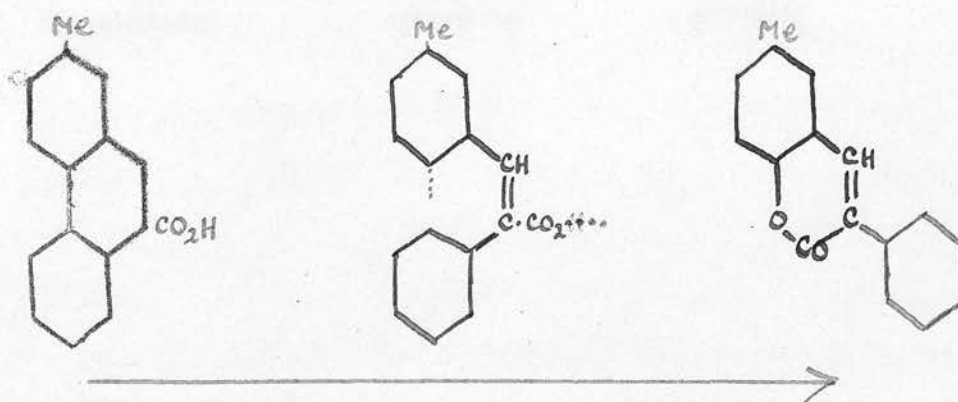


composition is altered to a mixture melting at  $112^{\circ}$  (A). Distillation of the mixture ( $106^{\circ}$ ) gives a product (m.p.  $118^{\circ}$  B) of different composition, containing less ethylphenanthrene and more by-product. When the authentic ethylphenanthrene (natural m.p.  $120^{\circ}$ ) is added to this, the melting point again falls to the eutectic point.



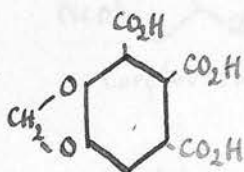
The nature of the by-product is of course very problematical. The author's experiences gained in the work of Publications 10 and 12 indicate two possible sources of impurity in Barger and Silberschmidt's synthetical preparation. It was found during the work described in those publications that the only method of obtaining satisfactory yields of phenanthrene-9-carboxylic acids was to diazotise with the calculated quantity of nitrite a solution of the amino-acid in methyl alcoholic sulphuric acid, and then to heat the diazonium solution under reflux. The by-product has possibly been found at this stage, since Barger and Silberschmidt heated the aqueous diazonium solution, and were unable to crystalline the product. Further, the author has found that the only suitable method of decarboxylating phenanthrene-9-carboxylic acids is to heat a solution in glacial acetic

acid in a sealed tube, and this is in harmony with the observations of other authors. It seems not improbable therefore that an alternative constitution for the by-product of Barger and Silberschmidt is either that of the methylester of a phenanthrenecarboxylic acid, similar to that which Pschorr obtained<sup>10</sup> by heating 3:4:5-tetramethoxyphenanthrene-9-carboxylic acid, or else that of an arylcoumarin like those which Mayer and Balle produced by the decarboxylation of 2-, 4-, or 5-methylphenanthrene<sup>11</sup> carboxylic acids. Stoermer and Prigge<sup>12</sup> showed that one of these, at any rate, was a coumarin, which owed its existence to a remarkable rupture of the central phenanthrene linkage.

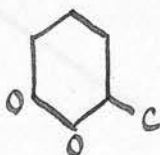


Domesticine and isodomesticine were considered by Kitasato<sup>13</sup> to be 3(4)-methoxy-4(3)-hydroxy-6:7-methylenedioxyaporphines because domesticine yielded 4:5-methylenedioxydenzene-1:2:3-tricarboxylic acid on oxidation, and their methylether, domestine, did not appear to be identical either with dicentrine or with

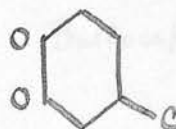
bulbocapnine methyl ether. The revision of the formula for laurotetanine leaves these alkaloids as the only examples of the vicinal grouping (below) among the aporphine alkaloids, and the author believes that further investigation will prove that domesticine and isodomesticine are really partially demethylated dicentrines, containing the usual homocatechol arrangement.



Acid from  
domesticine

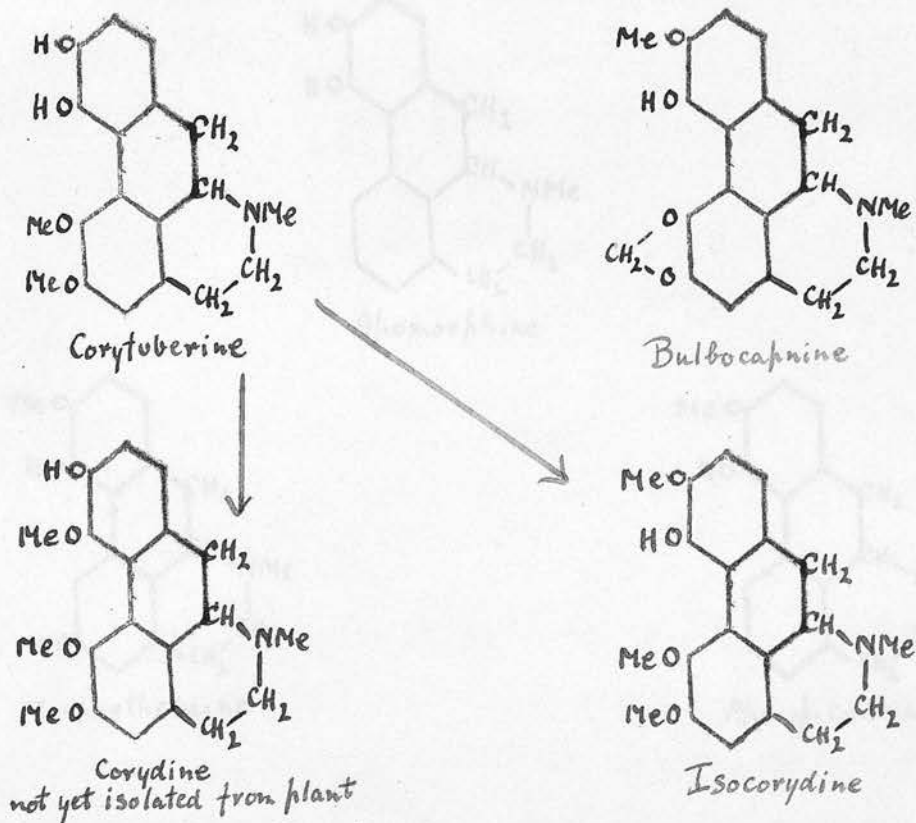


vicinal  
grouping



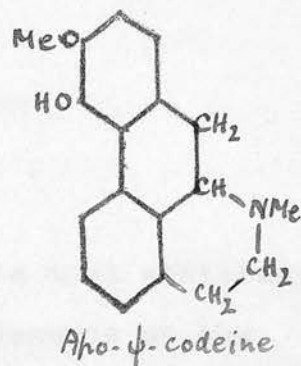
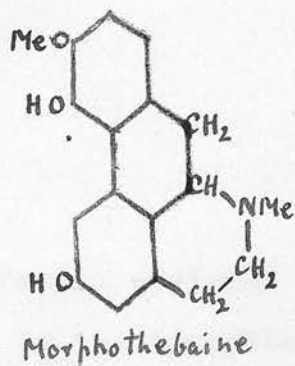
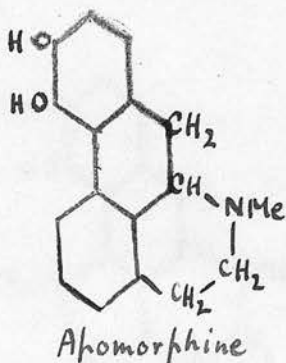
homocatechol  
grouping

B. Corytuberine Group. Isolated from *Corydalis Tuberosa*,  
and all dextro-rotatory.



Späth, Holter, and Posega<sup>14</sup> have established the relative position of the methoxyl and hydroxyl groups in bulbocapnine by oxidising its ethylether to 4-methoxy-3-ethoxybenzene-1:2-dicarboxylic acid of known constitution, and the synthesis of bulbocapnine methylether<sup>15</sup> (Publication 11) proves that these groups are in the 3:4 and not the 1:2 position in the phenanthrene nucleus. The similarity in the reactions of bulbocapnine and isocorydine with iodine (Pellagri) indicates C<sup>4</sup> as the position of the hydroxyl in isocorydine, and therefore C<sup>3</sup> in the isomeric corydine.

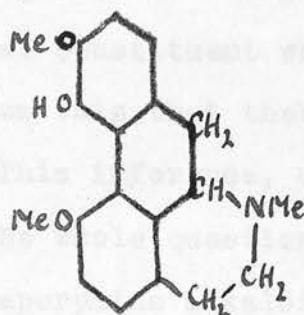
C. Derived Aporphines. All prepared from the Morphine Alkaloids, and all laevo-rotatory.



The laevorotatory character of these bases is noteworthy, and the question of this difference between the derived (from morphine) aporphines and the natural aporphines will be discussed shortly.



D. The Isothebaine Group. Contains only one member, which is dextrorotatory.

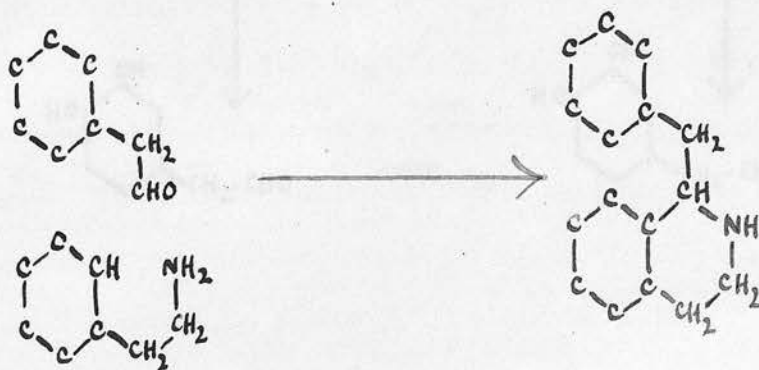


Isothebaine  
*Papaver orientale*

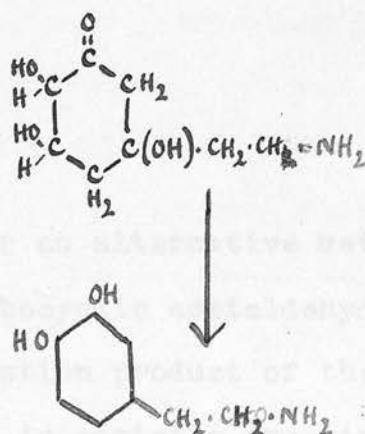
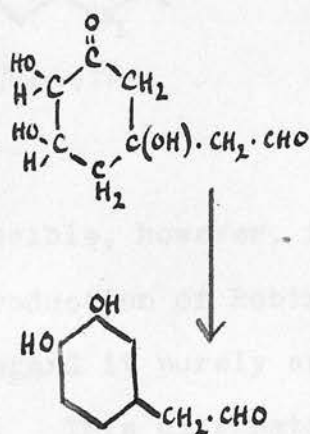
16

The formula assigned to isothebaine is the most arbitrary point in the aporphine series, since it depends on the degradation of the methylether to the picrate of a trimethoxyphenanthrene which is thought to be identical with the picrate of 3:4:5-trimethoxyphenanthrene, which, however, melts 6° higher. This identity, though attractive, is uncertain, and it is by no means excluded that isothebaine has the glaucine configuration in the "uppermost" benzene nucleus, although the fact that isothebaine gives the Pellagri reaction indicates a close similarity with corydine and morphothebaine, which are 3-methoxy-4-hydroxy-derivatives.

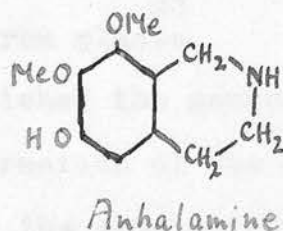
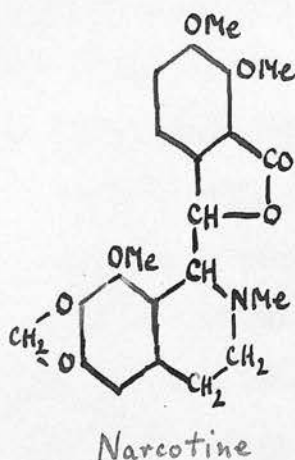
The point of chief interest in connection with isothebaine is that it occurs in the root of *Papaver orientale* after the period of blooming and withering of the aerial parts. During the time of vigorous growth of the plant, however, thebaine is the only alkaloidal constituent which can be isolated, and Klee has inferred from this that thebaine is actually converted into isothebaine. This inference, of which the accuracy is doubtful, opens up the whole question of the phytochemical synthesis of the morphine and aporphine alkaloids. This question has already been discussed in part or completely by Robinson, by Gadamer, and by Wellisch. Robinson's paper is of especial importance in view of its plausible, suggestive, and all-embracing character. It is the natural result of a study of the structures, relationships, and origins of the benzyl isoquinoline and phenanthrene alkaloids to agree with Robinson (loc. cit.) that the essential starting-points for the formation of these bases in the plant are a carbocyclic ethylamine and a carbocyclic acetaldehyde, which condense together following the lines of a Pictet isoquinoline synthesis.



Robinson has derived both of these necessary materials in a most ingenious manner from ammonia, formaldehyde, a reactive acetone derivative, and acetylglycollaldehyde. Using these simple substances, he arrives by facile stages at a hydroaromatic base and a hydroaromatic aldehyde, which may be dehydrated- to a dihydroxy- $\beta$ -phenylethylamine and a dihydroxyphenylacetaldehyde respectively:-



It is clear from the simultaneous occurrence in opium of the alkaloids morphine and narcotine that the basic constituent of the molecule must normally be present in its hydrated state, firstly because hydration of a benzene ring seems improbable, and secondly because in no other way can a satisfactory explanation be found of the presence of the three adjacent oxygen atoms of narcotine or of the anhalonium alkaloids.\* These views are essentially the same as those of Robinson.



It is possible, however, to consider an alternative method of the production of Robinson's carbocyclic acetaldehyde and to regard it purely as a degradation product of the proteins. This alternative scheme is strictly speaking

---

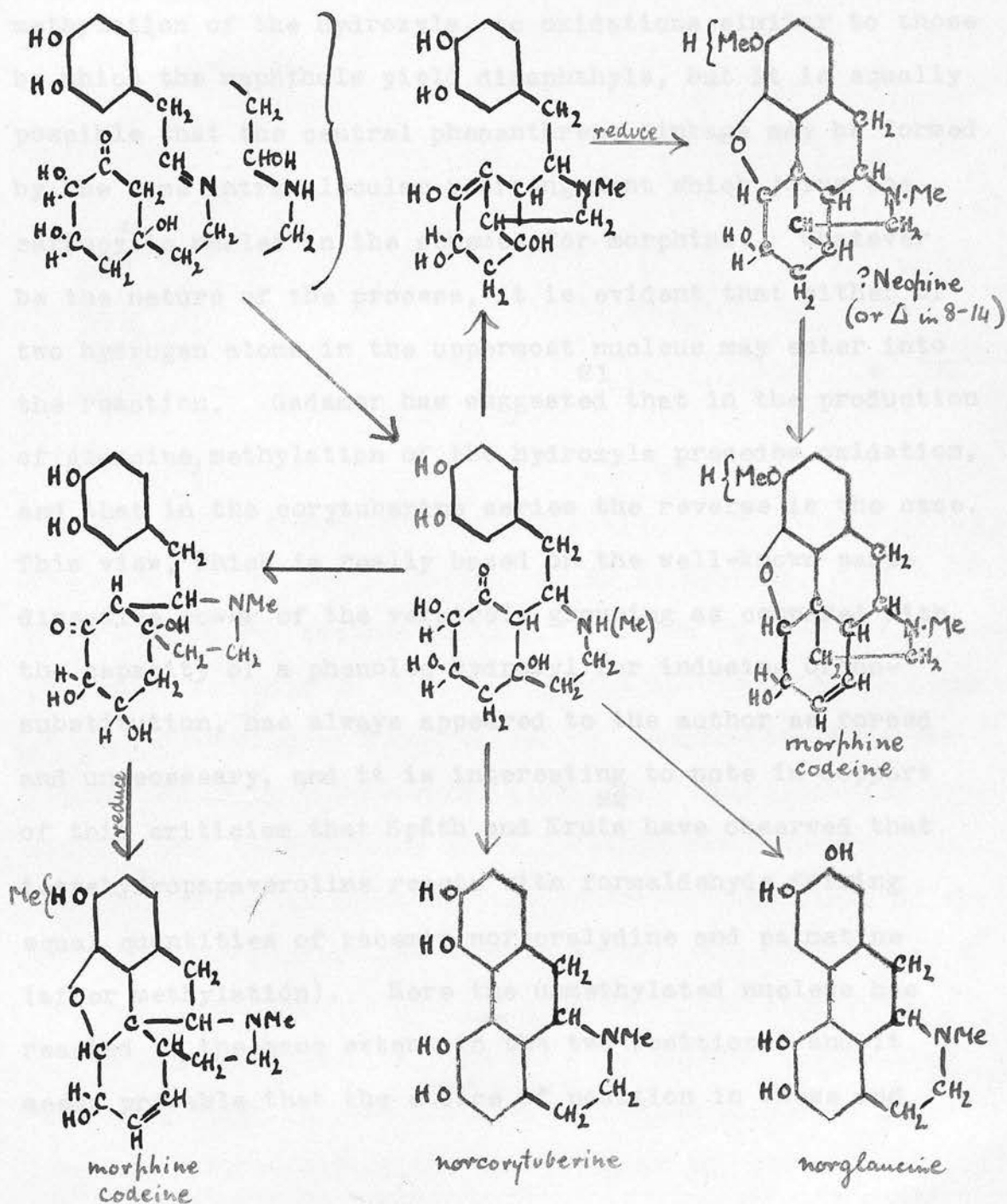
\* This example is introduced from an entirely different species (Anhalonium Lewinii, where the alkaloids occur in the flowering heads) in order to illustrate the general character of such phytochemical considerations.

unnecessary, since the intermediate steps of Robinson's synthesis may be regarded as the embryo stages of the production of tyrosine or of 3:4-dihydroxyphenylalanine in the plant. <sup>18</sup> Raper has shown that the initial action of tyrosinase <sup>20</sup> on tyrosine - a universal constituent of plant protein - is one of oxidation in which the homocatechol structure is produced in the form of 3:4 dihydroxyphenylalanine. Methylation of this amino-acid by means of formaldehyde as suggested by Robinson (loc.cit.), following the lines laid down by Hess, <sup>19</sup> would produce 3:4-dihydroxyphenylacetaldehyde, and in connection with this scheme it is noteworthy that 3:4-dihydroxyphenylalanine <sup>20</sup> has frequently been isolated from plants.

Having thus firmly established the general nature of the process which initiates the formation of the alkaloidal skeleton, the author proposes to turn to the consideration of a problem which appears to have been overlooked by most investigators. Gadamer <sup>1</sup> has drawn attention to this question but has not answered it. Why are the derived aporphines, apomorphine, morphothebaine, and  $\psi$ -apocodeine laevorotatory, whereas the natural aporphines are all dextrorotatory? To ensure clear understanding, it is necessary to indicate by schemes the possible steps in the synthesis by the plant of morphine, norcorytuberine, and norglaucine, but it must be realised that these schemes are not novel, but are adaptations and extensions

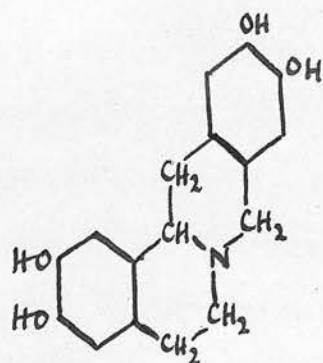


of Robinson's or Gadamers phytochemical processes applied to modern formulae.

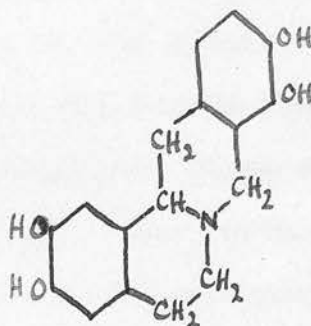


It is customary to regard the final stages in the formation of norcorytuberine and norglaucine, apart from the methylation of the hydroxyls, as oxidations similar to those by which the naphthols yield dinaphthyls, but it is equally possible that the central phenanthrene linkage may be formed by the same intramolecular rearrangement which joins the carbocyclic nuclei in the schemes for morphine. Whatever be the nature of the process, it is evident that either of two hydrogen atoms in the uppermost nucleus may enter into the reaction. <sup>21</sup> Gadamer has suggested that in the production of glaucine, methylation of the hydroxyls precedes oxidation, and that in the corytuberine series the reverse is the case. This view, which is really based on the well-known para-directive power of the veratrole grouping as compared with the capacity of a phenolic hydroxyl for inducing ortho-substitution, has always appeared to the author as forced and unnecessary, and it is interesting to note in support <sup>22</sup> of this criticism that Späth and Kruta have observed that tetrahydropapaveroline reacts with formaldehyde forming equal quantities of racemic norcoralydine and palmatine (after methylation). Here the unmethylated nucleus has reacted to the same extent in the two positions, and it seems probable that the choice of position in these and

similar cases is governed by the plant rather than by the alkaloid.



(nor)-Norcoralydine



(nor)-Palmatine

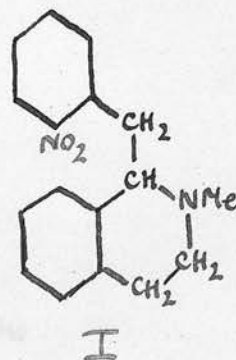
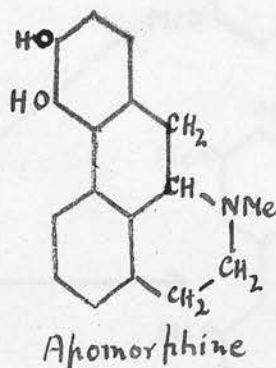
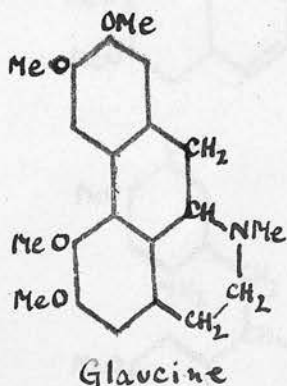
Returning now to the optical activity of the aporphines, one atom ( $C^9$ ) of the molecule only is asymmetric.\* By reference to the section on morphothebaine (p. 49) it will be seen that whatever be the processes involved in the formation of morphothebaine or apomorphine,  $C^9$  retains the same configuration as in the morphine alkaloid. The following conclusion must therefore be drawn. Since the hydrogen atom attached to  $C^9$  in morphine must be "below" the plane of the molecule (the hydrogen at  $C^{14}$  is above), the hydrogen at  $C^9$  must be "below" in the derived aporphines and therefore "above" in the natural aporphines. A natural sequence of this conclusion is that thebaine cannot be converted directly into isothebaine during the withering of the aerial parts of

\* The numbering is the same as in morphine.

*Papaver orientale*, but that the thebaine is destroyed, and that isothebaine is formed from fresh protein material. Thus it is evident that the fate of the alkaloidal skeleton is decided at the second stage of the Pictet isoquinoline synthesis (isomerisation or dehydration) since that step produces an asymmetric carbon atom. The further development of the isoquinoline to a morphine or an aporphine probably depends on the selective nature of biochemical processes, in which spatial configuration is known to play such an important part. It is, however, interesting to note one point in connection with the hydrindane formula which the author has considered as an alternative formula for morphine (p.47). When the isoquinoline structure is built up with tetrahedral models, the strain produced by forming the five membered carboxylic ring is much less if the hydrogen at C<sup>9</sup> is "below" the plane of the model (morphine configuration) than if it is "above" (aporphine configuration).

SYNTHETICAL EXPERIMENTS IN CONNECTION WITH THE  
 APORPHINE ALKALOIDS  
 -----

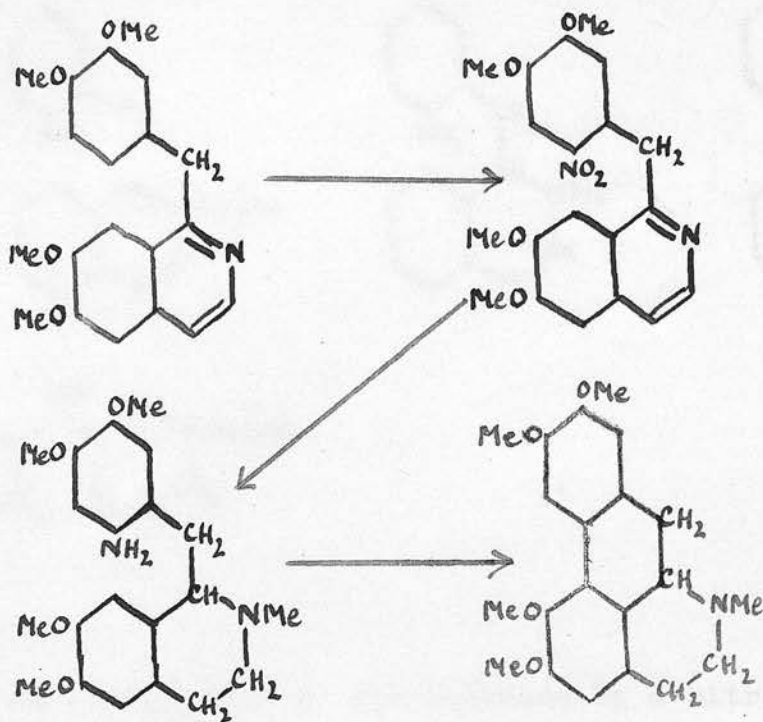
From a synthetical point of view, the aporphine bases which occur in Nature or are derived from morphine fall readily into two main divisions. These differ from each other with regard to the position occupied by the oxygen atoms in Ring I; glaucine is typical of the first group, while apomorphine is the simplest member of the second.



The most usual starting points in syntheses of aporphines which have been attempted in the past have been nitrobenzylisoquinolines (I), because the corresponding amino-derivatives<sup>24</sup> may be converted into the aporphines by Pschorr's method. The difficulty of preparing such nitrobenzylisoquinolines which has been experienced by various investigators has until now precluded the synthesis of the naturally occurring alkaloids with the exception of glaucine and dicentrine.<sup>25</sup> Since<sup>26</sup>



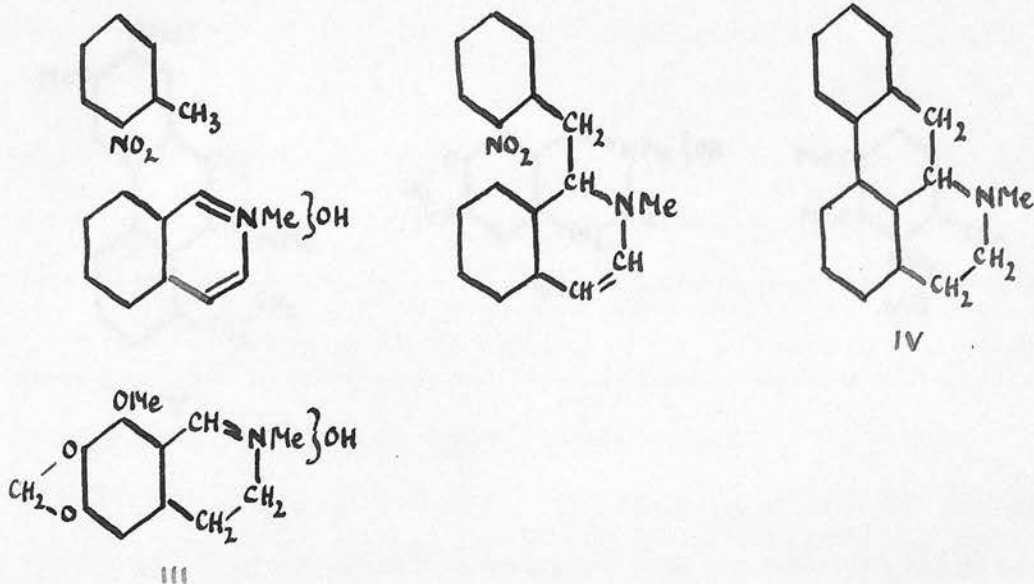
both these bases are exceptional in containing ethereal oxygen atoms in the 2:3-positions, the necessary nitroisoquinoline compound was readily prepared by the direct nitration of the requisite 1-benzylisoquinoline in which the 3':4'-positions were occupied by methoxy-groups. Thus, for example, papaverine (II) yielded 6-nitropapaverine which was converted into glaucine by Pschorr and by Gadamer.



On the other hand, many alkaloids of the aporphine group contain phenolic or ethereal oxygen atoms in the 3:4-positions, and the preparation of bases having this configuration by the method of direct nitration would involve the introduction of a nitro-group into the 2'-position of a substance such as

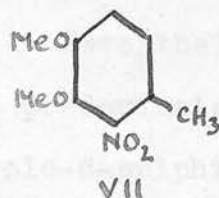
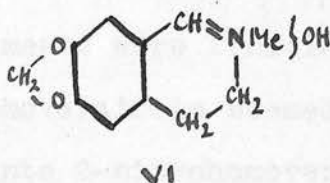
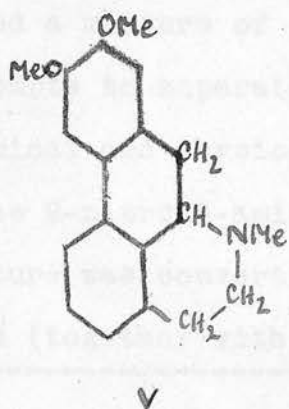
papaverine, - an operation which has not yet been accomplished.

The discovery by Hope and Robinson that cotarnine (III)<sup>27</sup> and the allied pseudo-bases condense with o-nitrotoluene and its derivatives provided a new method for the preparation of<sup>28</sup> nitrobenzylisoquinolines (I), and Gadamer, Oberlin, and Schoeler<sup>28</sup> have employed this method for the synthesis of aporphine (IV).



The replacement of nitrotoluene by a nitrohomoveratrole would lead in theory to the production of nitrodimethoxybenzylisoquinolines from which naturally occurring aporphines might be obtained, and in practice Robinson and his co-workers were<sup>29</sup> able to effect such a synthesis. Using 6-nitrohomoveratrole and quinoline methohydroxide they ultimately obtained isoapomorphine dimethylether (V);<sup>30</sup> this substance has the glaucine.

configuration in Ring I, but the extension of the method to the preparation of dicentrine was frustrated by the inability of hydrastinine (VI) to react with o-nitrotoluenes in presence of sodium ethoxide, whilst glaucine itself had already been obtained by Gadamer.



At this stage in the history of the subject the author initiated experiments on the synthesis of the aporphines and, in the first instance, turned his attention to the preparation of 2-nitrohomoveratrole (VII), which would lead in conjunction with suitable pseudo-bases to the production of alkaloids with the apomorphine configuration. This object proved remarkably difficult of achievement, since it was found to be impossible to introduce one nitro-group into the homocatechol molecule in the 2-position owing to the infinitely greater reactivity

exhibited at the 6-position (Publications 5 and 6). \*

Dinitration was however readily effected, and 2:6-dinitrohomoveratrole was obtained by the methylation of 2:6-dinitrocreosol (nitration of acetylcreosol) or 2:6-dinitroisocresol (nitration of isocresol in ether by nitrous fumes). \*\* The reduction by sodium sulphide of 2:6-dinitrohomoveratrole produced a mixture of the two possible nitroamines, and all attempts to separate this mixture into its components by chemical and physical means were fruitless. Nevertheless, since 2-nitro-6-aminohomoveratrole seemed to predominate, the mixture was converted into 2-nitrohomoveratrole-6-sulphinic acid (together with a large quantity of a complex by-product),

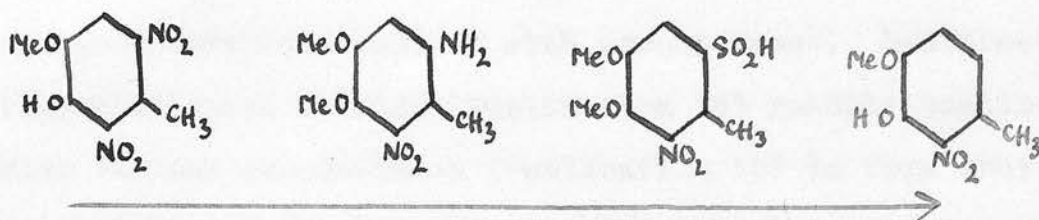
---

\* The following methods were investigated:

- (i) Nitration of isocresol in ether by means of fuming nitric acid: small quantity of indefinite product.
- (ii) Nitration of acetylcreosol; and of acetylisocresol; 6-nitroacetylcreosol; and 5-nitro-3-acetoxy-p-cresol and its methyl ether.
- (iii) Substitution in the 6-position by the chlorosulphonyl group followed by nitration: nitration in the 5-position.
- (iv) Nitration of acetyl-m-cresidine in acetic anhydride: 6-nitroacetyl-m-cresidine.
- (v) Diazotisation of m-cresidine in nitric acid: indefinite product.

\*\* This procedure has since been shown to be most valuable in the nitration of phenols.

which in its turn yielded 2-nitroisocresol by oxidation and distillation in superheated steam.



The methylation of this nitro-phenol yielded the oily 2-nitrohomoveratrole which was obtained at about the same date<sup>31</sup> by Oberlin, who employed somewhat similar methods. Unfortunately, however, no indications could be obtained that 2-nitrohomoveratrole reacted with pseudo-bases under a variety of experimental conditions, and this remarkable difference as regards the activating effect of the nitro-group in the two positions is paralleled by an instance in Publication 18.

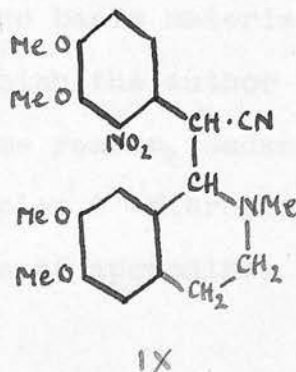
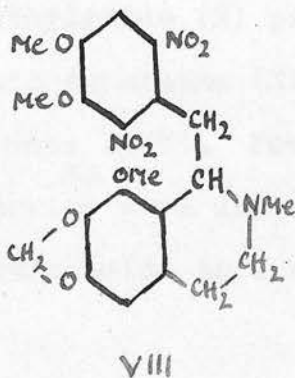
On the other hand, derivatives of dinitrotoluene readily condense with pseudo-bases, as for example when 2:6-dinitrohomoveratrole forms anhydrocotarnine-2:6-dinitrohomoveratrole (VIII) on being warmed with cotarnine in alcoholic solution (Publication 5). This modification of procedure however seems to introduce great practical difficulties in the preparation of the necessary bases of the type of 1-(2'-aminobenzyl)-2-methyltetrahydroisoquinoline (I, in which  $-\text{NO}_2$  is replaced by  $-\text{NH}_2$ ), as may be seen by comparison with the analogous

---

\* Selective reduction and elimination of one nitro-group, followed by reduction of the other.



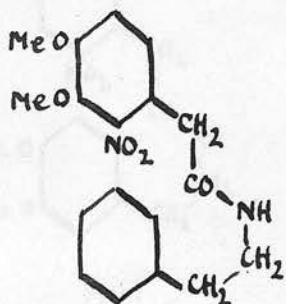
experiments of Robinson and Shinoda. The author therefore decided to explore methods which did not involve selective reduction, and the reactivity of the methylene group of benzyl cyanide offered a possible means of uniting the 2-nitrohomoveratrole nucleus with pseudo-bases. 2-Nitro-3:4-dimethoxybenzyl cyanide (Publication 16) readily combines with various pseudo-bases (Publication 15) to form anhydro-derivatives of which anhydrolaudaline 2-nitro-3:4-dimethoxybenzyl cyanide (IX) is characteristic.



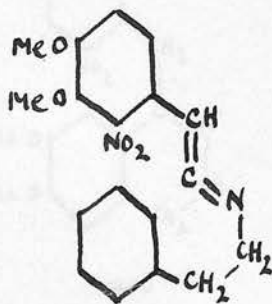
Unfortunately the conversion of these bases into derivatives of phenanthrene was frustrated, by their instability to reagents. Cold, dilute acid immediately separates the molecule into its generators, and it was found impossible to reduce the nitro-group in alkaline media without simultaneously removing the benzyl cyanide residue by hydrolysis. The author

therefore abandoned attempts to prepare nitrobenzylisoquinolines by means of pseudo-base condensations, and turned to what has proved a more satisfactory method.

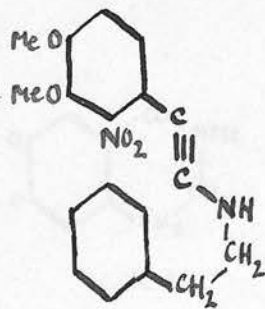
A review of the literature convinced the author that the Bischler-Napieralski<sup>33</sup> synthesis of isoquinoline bases had not been sufficiently investigated in connection with the aporphine<sup>34</sup> alkaloids. The observations made by Pictet and Kay in 1913 during an attempt to synthesise apomorphine dimethyl ether by a modification of this method showed that the action of phosphorus pentoxide on 2'-nitro-3':4'-dimethoxyphenylaceto- $\beta$ -phenylethylamide (X) produced no basic material but only a non-basic substance (XI), to which the author prefers to assign the formula (XII). For the same reason, Gadamer, Oberlin,<sup>35</sup> and Schoeler were unable to employ 2'-nitrophenylaceto- $\beta$ -phenylethylamide in a synthesis of aporphine.



X

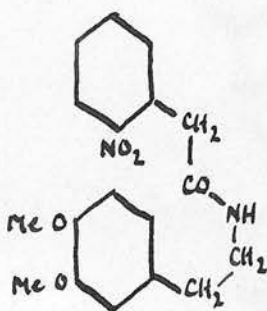


XI

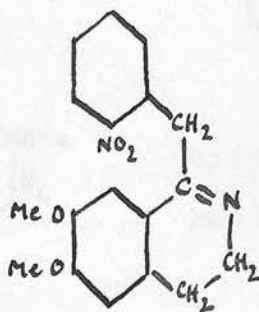


XII

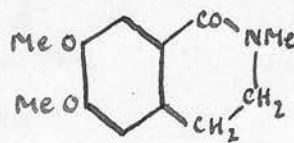
The amides which have just been mentioned are similar in that they contain no activating groups in the phenylethylamine residue, and it was hoped that the Bischler-Napieralski synthesis would proceed more smoothly in the case of an amide, such as 2'-nitrophenylaceto- $\beta$ -3:4-dimethoxyphenylethylamide (XIII), in which the methoxy-groups would facilitate the formation of an isoquinoline. This expectation was justified, since 2'-nitro-5:6-dimethoxy-1-benzyl-3:4-dihydroisoquinoline (XIV) was obtained in excellent yield by the action of phosphorus pentachloride on a cold solution of the amide (XIII) in chloroform (Publication 9). The constitution of this base was proved by the fission of its methiodide with dilute sodium <sup>36</sup>hydroxide in the manner described by Pschorr, the products of this reaction being o-nitrotoluene and 6:7-dimethoxy-2-methyl-3:4-dihydroisoquinoline (XV).



XIII

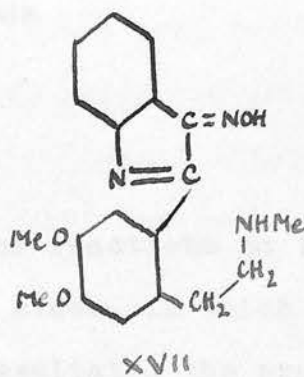
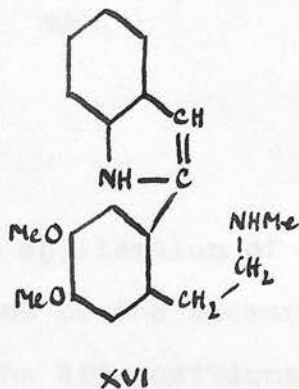


XIV



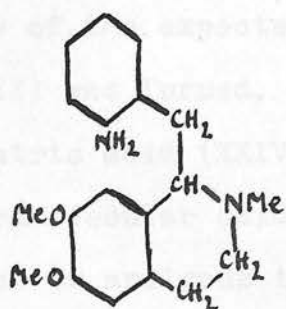
XV

When the methiodide of the base (XIV) was reduced with zinc dust and sulphuric acid in faintly acid solution, the monoacidic 2-(4':5'-dimethoxy-2'- $\beta$ -methylaminoethyl)phenyl-indole (XVI) was formed. This substance, which yielded a monohydrochloride and a non-basic acetyl derivative, exhibited the colour reactions of an indole, and yielded a deep red solution when treated with nitrous acid. From this solution the 3-oximino-derivative (XVII) was isolated; this substance is soluble in sodium hydroxide solution, dissolves in dilute mineral acids with the production of a red colour, and does not give the Liebermann nitroso-reaction. It is as yet unexplained why the nitrous acid attacks the indole nucleus in preference to the basic methylamino-group.

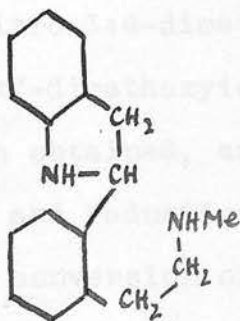


On the other hand, the reduction of the methiodide of the base (XIV) in strongly acid solution with zinc dust and hydrochloric acid yielded the diacidic 2'-amino-6:7-dimethoxy-1-benzyl-2-methyltetrahydroisoquinoline (XVIII), which formed

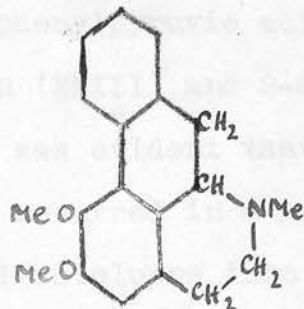
a dihydrochloride and a basic acetyl-derivative, and could be diazotised. From the same reduction, a small amount of 2-(4':5'-dimethoxy-2'- $\beta$ -methylaminoethyl)phenyldihydroindole (XIX) was isolated, and formed a dihydrochloride and a nitrosamine. The base (XVIII) was converted into 5:6-dimethoxy-aporphine (XX) by treating the diazonium sulphate with copper powder or by heating it with methyl alcohol.



XVIII



XIX

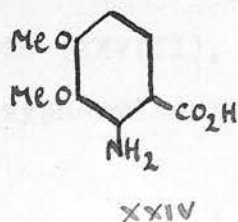
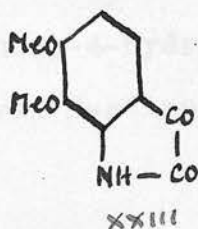
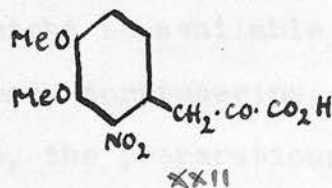
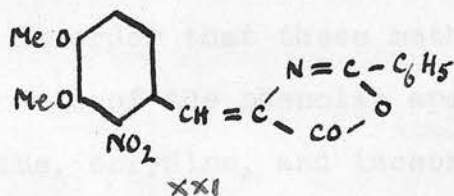


XX

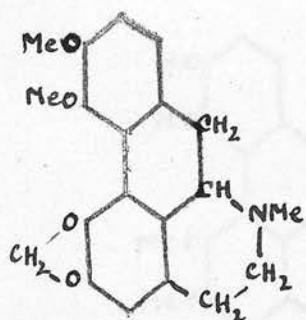
The application of similar reactions to the synthesis of aporphines of the apomorphine class, in which the oxygen atoms are in the 3:4-positions, necessitated the preparation of very large quantities of 2-nitro-3:4-dimethoxyphenylacetic acid. This acid had been obtained from vanillin by Kay and Pictet,<sup>34</sup> but the process involved eight stages including a Cannizaro



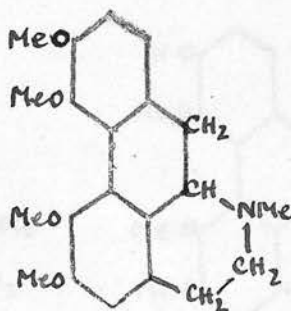
reaction in which the required product was the alcohol, and it was therefore desirable to investigate more convenient methods of obtaining this essential material. The well-known<sup>37</sup> preparation of phenylacetic acids devised by Erlenmeyer and<sup>38</sup> by Mauthner had never been applied to a nitroaldehyde, and accordingly the azlactone (XXI) prepared from 2-nitroveratraldehyde and hippuric acid was submitted to alkaline hydrolysis (Publication 16). The course of the reaction was abnormal; none of the expected 2-nitro-3:4-dimethoxyphenylpyruvic acid (XXII) was formed, but 6:7-dimethoxyisatin (XXIII) and 2-amino-<sup>34</sup>veratric acid (XXIV) were obtained, and it was evident that intramolecular oxidation and reduction had occurred in a manner which is analogous to the conversion of o-nitrotoluene into anthranilic acid. No alternative remained, therefore, but to employ the method of Kay and Pictet<sup>34</sup> for the preparation of 2-nitro-3:4-dimethoxyphenylacetic acid, and considerable modifications are described in Publication 16 which permit the production of this acid to be carried out on a large scale.



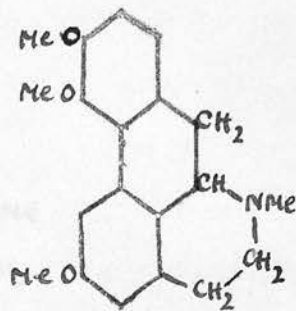
The reactions which are described in the preceeding pages were then extended to the synthesis of bulbocapnine methyl-ether (XXIV), corytuberine dimethylether (XXV), and morphothebaine dimethylether (XXVI), by employing 2-nitro-3:4-dimethoxyphenylacetic acid and suitable  $\beta$ -phenylethylamines as starting materials, and these researches are described in Publications 11, 13, and 14 respectively (compare Späth and<sup>41</sup> Hromatka).



XXIV



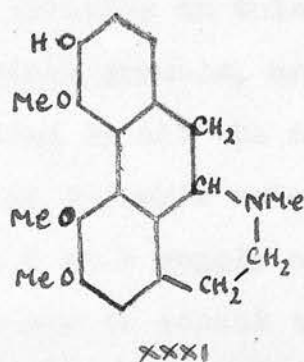
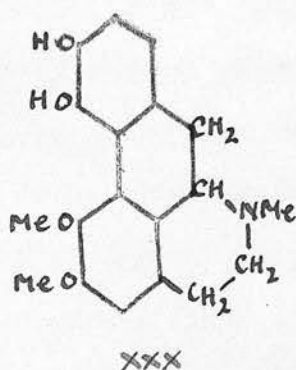
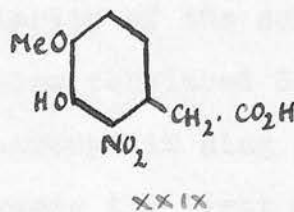
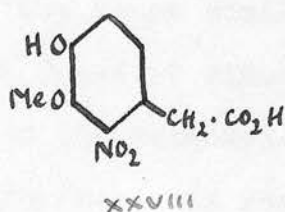
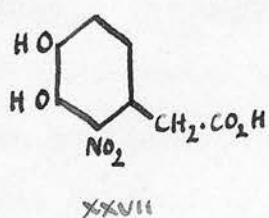
XXV



XXVI

In order that these methods might be available for the synthesis of the phenolic aporphines, corytuberine, bulbocapnine, corydine, and isocorydine, the preparations of 2-nitro-3:4-dihydroxyphenylacetic acid (XXVII), of 2-nitro-3-methoxy-4-hydroxyphenylacetic acid (XXVIII), and of the isomeric 2-nitro-3-hydroxy-4-methoxyphenylacetic acid (XXIX)

have been investigated with some care, and the practical details are described in Publication 16. Syntheses of corytuberine (XXX) and corydine (XXXI) (Publication 17) are rapidly approaching completion.



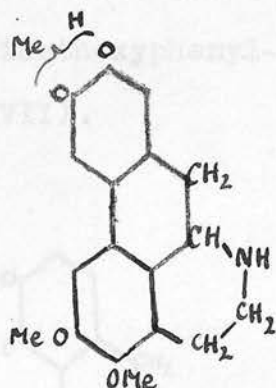
Until November 1928, the constitutions assigned to laurotetanine (XXXII) and its dimethyl-derivative, isoglaucine, (XXXIII) were those devised by Gorter.<sup>5</sup> The main arguments from which he deduced these structures were twofold. In the first place, the oxidation of laurotetanine by alkaline permanganate yielded 1:2-dimethoxybenzene-3:4:5-tricarboxylic acid, thus establishing the fact that the benzene ring of the isoquinoline part of the molecule was a derivative of catechol.

This acid may however be obtained from glaucine and from corytuberine, and Gorter's choice of the orthohomocatechol grouping in Ring III depended on the fact that isoglaucine was not identical with glaucine or with corytuberine dimethyl-ether. Secondly, the close similarity of the colour reactions of isoglaucine with those of glaucine convinced Gorter that the configuration of the methoxyl-groups in Ring I was the same as that in glaucine. As regards the first point, it has already been stated (p. 94) that the author considers the occurrence of the vicinal grouping in this series to be highly improbable on phytochemical grounds, and a comparison of the colour reactions exhibited by all the members of the aporphine group assured him that Gorter's second argument was entirely valueless. In default of a supply of laurotetanine<sup>\*</sup>, the author decided some months ago to attack the problem by synthesising the base (XXXIII) and the isomeric 3:4:6:7-tetramethoxyaporphine (XXXIV). These experiments are described in Publication 18, and it clear that neither of the substances (XXXIII) or (XXXIV) resembles Gorter's isoglaucine. Incidentally it may be mentioned that the colour reactions of the base (XXXIV) approximate more closely to those of glaucine than do those of "isoglaucine" (XXXIII). These

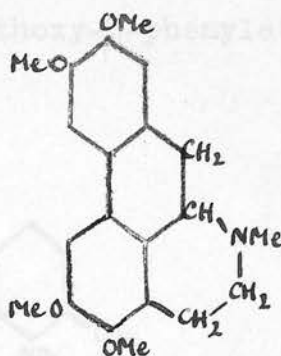
---

\* This alkaloid is obtained from the bark of *Litsea citrata* from Java.

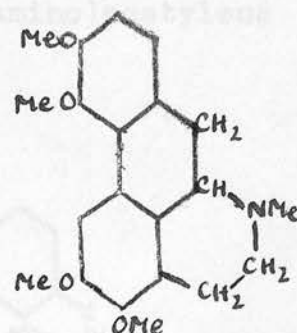
results are in <sup>39</sup>complete agreement with the very recent work <sup>40</sup>of Barger and Silberschmidt and of Späth and Strauhal, who have shown that laurotetanine is in reality a member of the glaucine group (p. 90) and that Gorter's "isoglaucine" was impure glaucine.



XXXII



XXXIII

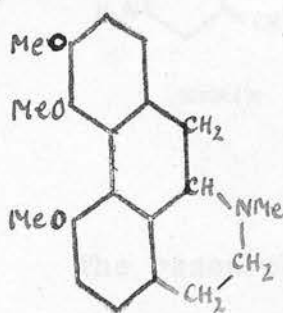


XXXIV

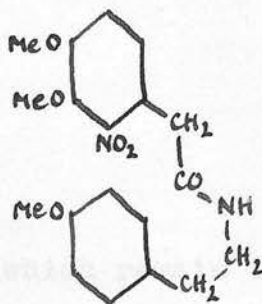
In Publication 19 are recorded two groups of experiments, unfortunately not successful, by which it was hoped to solve the problem of the constitution of isothebaine by the synthesis of the substance having the formula usually assigned to its methyl ether <sup>16</sup>(XXXV). The first group consisted of a large number of attempts to convert 2'-nitro-3':4'-dimethoxyphenyl-aceto-β-4-methoxyphenylethylamide (XXXVI) into the corresponding isoquinoline base, since it was hoped that the presence of the methoxyl group in the phenylethylamine nucleus would



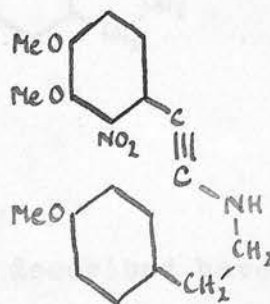
raise the general reactivity of the molecule sufficiently to allow the Bischler-Napieralski reaction to proceed normally. This expectation was not realised; no basic material was formed during the reactions, and the only crystalline substance which could be isolated was the neutral 2'-nitro-3':4'-dimethoxyphenyl-(4-methoxy- $\beta$ -phenylethylamino)acetylene (XXXVII).



XXXV



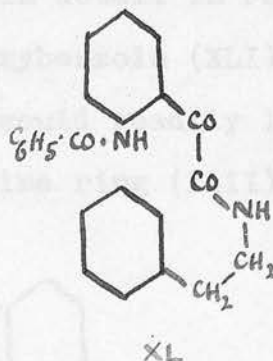
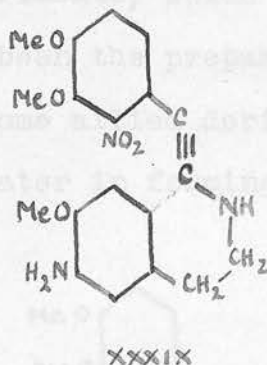
XXXVI



XXXVII

These failures were attributed to insufficient activation of the 2-position of the  $\beta$ -phenylethylamine nucleus, so that it was unable to compete with the methylene group of the acyl residue, the reactivity of which is enhanced by the nitro-group. In the hope of overcoming these difficulties, the second group of experiments <sup>was</sup> ~~were~~ devised, in which an acyl-amino-group was introduced into the 3-position of the

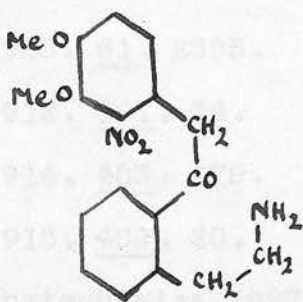
phenylethylamine. These efforts, however, were no more successful than those previously described and only resulted in the formation of 2'-nitro-3':4'-dimethoxyphenyl-(3-amino-4-methoxy- $\beta$ -phenylethylamino)acetylene (XXXIX).



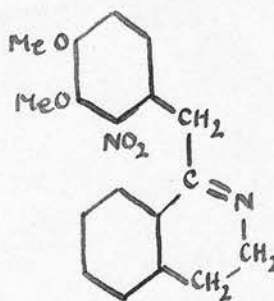
The researches which remain to be described have dealt with attempted syntheses of apomorphine dimethylether (Publication 20). In the first place, the experiments of Kay and Pictet (p. 113) were repeated and confirmed, and as their miscarriage was due to the presence of the methylene group of the acyl residue, several attempts, unfortunately unsuccessful, were made with the object of converting 2-benzoylaminophenylglyoxyl- $\beta$ -phenylethylamide, (XL) into an isoquinoline derivative. Had these results proved more satisfactory, the method might have been extended to 6-7-dimethoxyisatin (p. 117)

A considerable volume of work has also accumulated (Publication 20), in which efforts have been made to devise

a new method for the synthesis of apomorphine dimethylether, which would be applicable to the production in the laboratory of those aporphines where the activation of the  $\beta$ -phenylethylamine nucleus is insufficient. The idea underlying these experiments, which are described in detail in Publication 20, has been the preparation of a deoxybenzoin (XLI) or benzil, or some allied derivative, which would readily lose the element of water in forming the isoquinoline ring (XLII).



XLI



XLII

# REFERENCES.

1. Arch. Pharm. 1915. 253. 266.
2. Ber. 1906. 39. 3124.
3. Arch. Pharm. 1911. 249. 680.
4. Arch. Pharm. 1921. 259. 135.
5. Bull. Jard.bot. Burtenzorg. 1921.(iii). 3. 180.
6. Ber. 1925. 58. 2768.
7. Gadamer. Arch. Pharm. 1911. 249. 503.
8. J. 1928. 2919.
9. Ber. 1928. 61. 2395.
10. Ann. 1912. 391. 54.
11. Ann. 1914. 403. 178.
12. Ann. 1915. 409. 20.
13. Acta Phytochimica 1927. 3. 175.
14. Ber. 1928. 61. 322.
15. Späth and Hromatka. Ber. 1928. 61. 1334.
16. Gadamer and Klee. Arch. Pharm. 1911. 249. 39.  
Klee. Arch. Pharm. 1914. 252. 211.
17. J.C.S. 1917. 111. 892.
18. Biochem. J. 1927. 21. 89; Fermentforsch. 1927. 9. 206.
19. Ber. 1913. 46. 4104.
20. Osborne, The Vegetable Proteins. 1919.  
Plimmer, The Chemical Constitution of the Proteins. 1917.
21. Arch. Pharm. 1911. 249. 498.
22. Sitzungsberichte der Akad. der Wiss. Wien. 1928. 137. 817.

23. Pictet and Spengler. Ber. 1911. 44. 2030.
24. Ber. 1896. 29. 496.
25. Gadamer Arch. Pharm. 1911. 249. 680.  
Pschorr Ber. 1904. 37. 1926.
26. Haworth, Perkin, and Rankin J. 1925. 127. 2018.
27. J. 1911. 99. 2114.
28. Arch. Pharm. 1925. 263. 8.
29. Hope and Robinson, loc.cit.  
Graesser-Thomas, Gulland, and Robinson, J. 1926, 1971.  
Robinson and West, ibid. p. 1985.  
Robinson and Shinoda ibid. p. 1987.
30. Robinson and Robinson, J. 1911. 105. 1456.
31. Arch Pharm. 1925. 263. 641.
32. J. 1926, 1987.
33. Ber. 1893. 26. 1903.
34. J. 1913. 103. 950.
35. loc.cit.
36. Ber. 1904. 37. 1932.
37. Ann. 1892. 271. 164; 1904. 337. 265.
38. Ann. 1909. 370. 368.
39. J. 1928, 2924.
40. Ber. 1928. 61. 2395.
41. Ber. 1928. 61. 1334, 1692.



No literature on the morphine and morphine alkaloids would be complete without a short reference to sinomenine, an alkaloid which was first isolated from the root of the Japanese climbing plant *Sinomenis* (L.) by Kishi, Oishi, and Sakajima (*J. Pharm. Soc. Japan*, 1933, 53, 511), and which has been examined more fully by Sato (*Proc. Imp. Acad. Tokyo*, 1933, 9, 387, 414).

#### ADDENDUM.

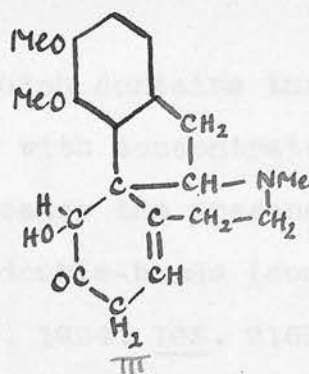
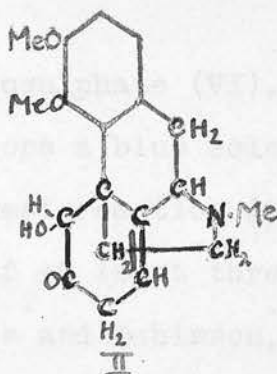
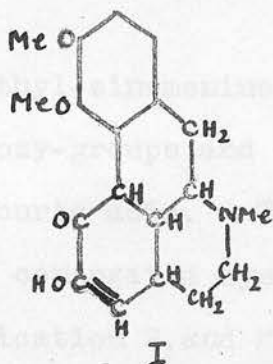
#### THE CONSTITUTION OF SINOMENINE.

On the basis of these and other experiments (see below), Sato assigned to sinomenine the structure (I), but a consideration of other properties of the alkaloid convinced the author that the formula (II), or possibly (III), is a more suitable representation. On this basis, dehydrosinomenine is a diketone, and the inability of the second carbon group to form an oxime or carbazone is probably analogous to the failure of the ketone group in the case position of dehydrocorticosterone, theobromine, or 4-hydroxyacetophenone to react with hydroxylamine.

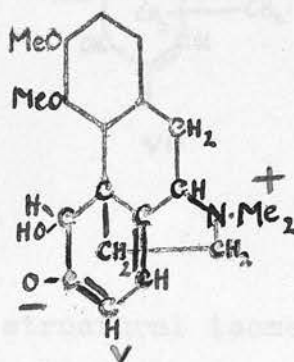
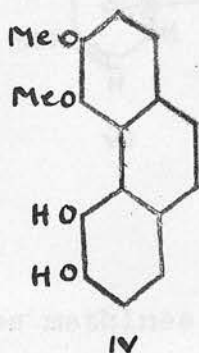
No treatise on the morphine and aporphine alkaloids would be complete without a short reference to sinomenine, an alkaloid which was first isolated from the root of the Japanese climbing-plant *Sinomenium acutum* by Kondo, Ochiai, and Nakajima (J.Pharm.Soc. Japan, 1923. 497. 511), and which has been examined more fully by Goto (Proc. Imp. Acad. Tokyo, 1926. 2. 7, 167, 414).

Sinomenine,  $C_{19}H_{23}O_4N$ , is an unsaturated ketonic alcohol, containing two methoxyl- and one methylimino-groups, which exhibits the intense colour reactions of phenols though not itself phenolic. Catalytic reduction yields a ketonic dihydro-derivative, of which the colour reactions are undiminished, and oxidation by mild reagents removes two hydrogen atoms forming dehydrosinomenine, which yields a monoxime and a monosemicarbazone and still exhibits vivid colour reactions.

On the basis of these and other experiments (see below), Goto assigned to sinomenine the structure (I), but a consideration of other properties of the alkaloid convinced the author that the formula (II), or possibly (III), is a more suitable representation. On this basis, dehydrosinomenine is a diketone, and the inability of the second carbonyl group to form an oxime or semicarbazone is probably analogous to the failure of the methylene group in the same position of dihydrothebainone, thebainol, or dihydrohydroxythebainone to react with benzaldehyde.

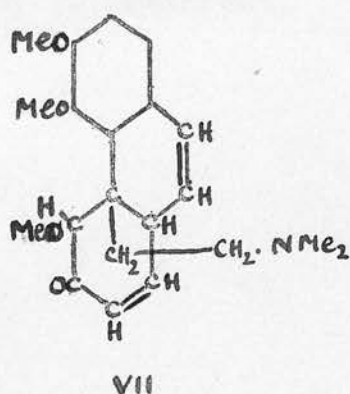
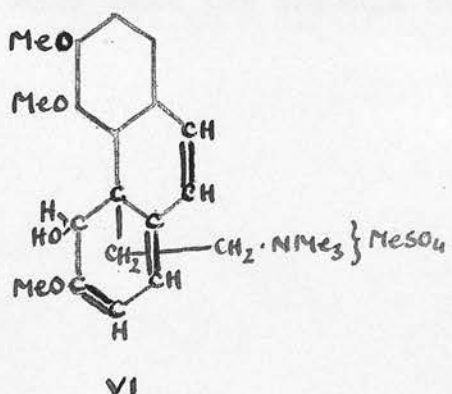


When sinomenine is heated with concentrated potash, sinomenol (probably IV) is formed together with methyl-ethylamine, and a similar result is observed using sinomenine methiodide. The similarity of this result with the behaviour of the morphine alkaloids in analogous circumstances proves that the ethanamine chain of sinomenine is attached to C<sup>13</sup> or C<sup>14</sup>, thus forming a direct barrier to the production of an aromatic phenanthrene system in which it would be retained as a normal side-chain.

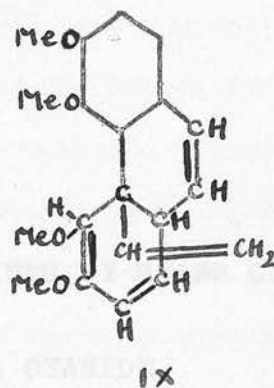
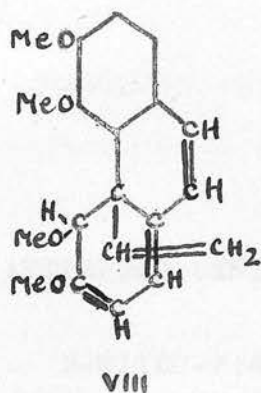


The Hoffmann degradation of sinomenine methiodide yields first an anhydro-base (V), which is readily decomposed by cold sodium hydroxide and methyl sulphate forming

$\alpha$ -methyl-sinomenine methosulphate (VI), which contains three methoxy-groups and develops a blue colour with concentrated sulphuric acid. This last reaction indicates the presence of a conjugated system of at least three double-bonds (compare Publication 2, and Menzies and Robinson, J. 1924. 125. 2163). The same  $\alpha$ -methylsinomeninemethine may be prepared directly from sinomenine by means of methyl sulphate and sodium hydroxide, but in this case it is accompanied by a second methine,  $\beta$ -methylsinomeninemethine (VII), which develops an orange-red colour with concentrated sulphuric acid.



These methines are therefore structural isomerides, and this conclusion is confirmed by the fact that further exhaustive methylation converts them into two isomeric tetramethoxyvinyl-dihydrophenanthrenes, (VIII) and (IX) respectively.



Since the changes which have been described above cannot be satisfactorily explained in the light of Goto's formula, it would seem that the formula itself is incorrect.



PUBLICATION 15  
-----

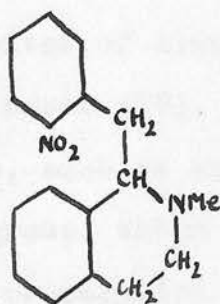
ATTEMPTED SYNTHESSES OF APORPHINES BY MEANS OF  
2-NITRO-3:4-DIMETHOXYBENZYL CYANIDE.  
-----

The whole of the work described in this paper was  
carried out personally by the author.

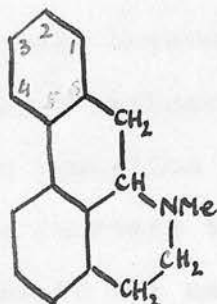


Many alkaloids of the aporphine group contain phenolic  
or ethereal oxygen in the 3:4-positions, and in order  
to prepare bases of this constitution by the method of

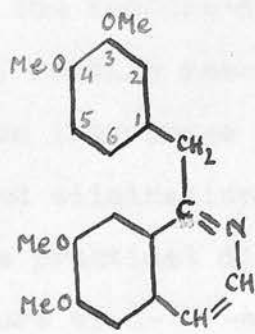
The most usual starting points in attempts to synthesise aporphine alkaloids have been substituted nitro-benzylisoquinolines (I), because these bases on reduction yield the corresponding amino-derivatives, which may be converted by Pechorr's method (Ber., 1896, 29, 496) into the phenanthrene alkaloids. The difficulty of preparing such nitroisoquinolines (I) has in general precluded the synthesis of the naturally occurring alkaloids with a few exceptions. These exceptions are unique, however, in containing ethereal oxygen atoms in the 2:3-positions (II) and the necessary nitroisoquinoline bases are readily prepared by direct nitration of the requisite 1-benzylisoquinoline derivative in which the 3':4'-positions are occupied by methoxyl-groups (III).



I



II

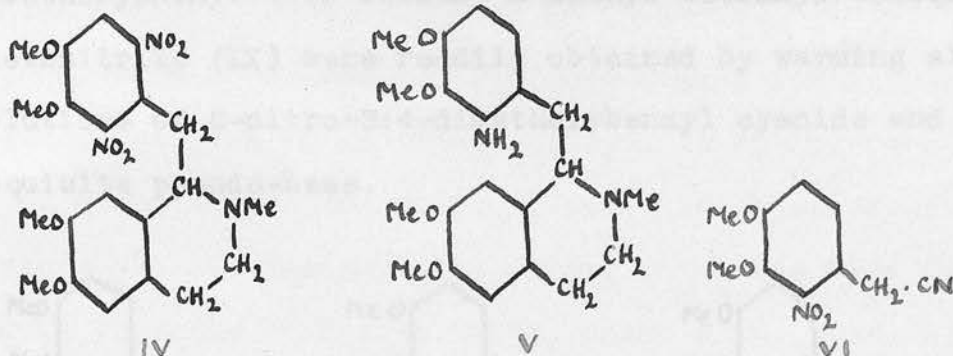


III

Many alkaloids of the aporphine group contain phenolic or ethereal oxygen in the 3:4-positions, and in order to prepare bases of this constitution by the method of

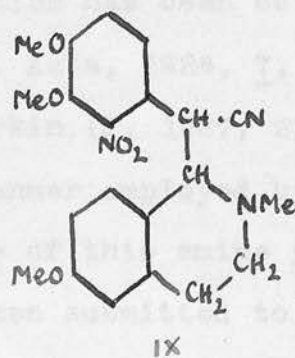
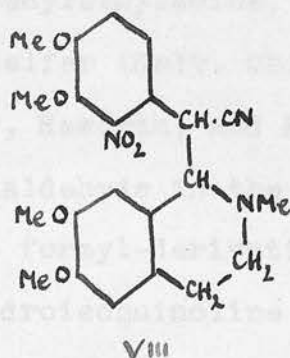
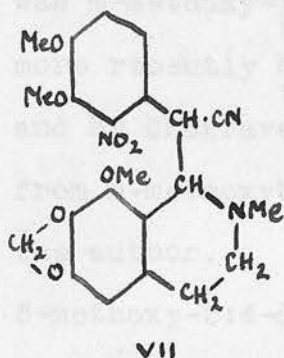
direct nitration, it would be necessary to introduce a nitro-group into the 2'-position of a base of the papaverine class (III) - an operation which has not yet been accomplished.

The discovery by Hope and Robinson (J. 1911, 99, 2114), that cotarnine and the allied pseudo-bases condense with derivatives of o-nitrotoluene, provided a new method for the preparation of bases of the class (I), which has been employed by Gadamer, Oberlin, and Schoeler (Arch. Pharm. 1925, 263, 81) for the synthesis of aporphine (II). It has not yet been applied to the synthesis of the naturally occurring alkaloids of the series, partly owing to the inability of some pseudo-bases, such as hydrastinine, to condense with derivatives of o-nitrotoluene, and partly on account of the inactivity of the methyl group of 2-nitro-homoveratrole as compared with that of the 6-nitro-derivative. Derivatives of dinitrotoluene, however, readily react with pseudo-bases (IV), but this modification introduces complications, such as selective reduction and elimination of one nitro-group, which greatly increase the practical difficulties in the preparation of bases of the nature of 1-(2'-aminobenzyl)-2-methyltetrahydroisoquinoline (V).



It seemed possible that these difficulties might be circumvented by the use of a mononitro-derivative of toluene<sup>ve</sup>, in which the methyl group was activated in such a manner, firstly that no interference with the reduction of the nitro-group would occur, and secondly that the activating group might subsequently be removed without affecting the rest of the molecule. Experiments along these lines indicated that 2-nitro-6-bromohomoveratrole (Publication 6) was in no way more reactive than the non-brominated substance, and attention was therefore directed to 2-nitro-3:4-dimethoxybenzyl cyanide (VI). It seemed probable that the methylene group of this substance would exhibit the same high capabilities for condensation as are shown by that of benzyl cyanide (compare Frost, Ann. 1889, 250, 157; Edwards, J. 1926, 744). This expectation was fully justified, and anhydrocotarnine-2-nitro-3:4-dimethoxybenzyl cyanide (VII), anhydrolaudaline-2-nitro-3:4-dimethoxybenzyl cyanide (VIII) and 2'-nitro-3':4'-

dimethoxyphenyl-1-(6-methoxy-2-methyl-tetrahydroisoquinoline) acetonitrile (IX) were readily obtained by warming alcoholic solutions of 2-nitro-3:4-dimethoxybenzyl cyanide and the requisite pseudo-base.



The subsequent treatment of such anhydro-compounds was intended to be reduction of the nitro-group, completion of the phenanthrene system by diazotisation, hydrolysis of the cyano-group by Pinner's method (Die Imidoäther, 1892), and elimination of the resulting carboxyl group by distillation under highly-reduced pressure. Unfortunately, this sequence broke down at the first stage (reduction), because the anhydro-derivatives were immediately hydrolysed by cold dilute acids with re-formation of their generators, and it was found impossible to effect the reduction of the nitro-group in alkaline media without causing simultaneous fission of the molecule, as is described in the experimental section.



Some description is required of the stages in the production of 6-methoxy-1-hydroxy-2-methyltetrahydroisoquinoline, the pseudo-base employed in the preparation of the base (IX). The starting point in these experiments was m-methoxy- $\beta$ -phenylethylamine, which has been obtained more recently by Helfer (Helv. Chim. Acta, 1924, 7, 945) and by Chakravarti, Haworth, and Perkin (J. 1927, 2265) from m-methoxybenzaldehyde in the manner employed by the author. The formyl-derivative of this amine yielded 6-methoxy-3:4-dihydroisoquinoline when submitted to the Bischler-Napieralski reaction (Ber. 1893, 26, 1903), and the pseudo-base was readily obtained from this by treatment of the methiodide with aqueous potash. A number of related substances are described in the experimental section.

#### EXPERIMENTAL

m-Methoxy- $\omega$ -nitrostyrol. This substance was prepared in the hope that m-methoxy- $\beta$ -phenylethylamine might easily be obtained from it by reduction. The yield during this latter process was unsatisfactory, and the method was abandoned.

(i) A cold solution of sodium (2.3g) in absolute alcohol (50cc.) was added during one hour to a solution of m-methoxybenzaldehyde (12.4g) and nitromethane (6.1g) which was

cooled in ice. After the mixture has remained in ice until a sample deposited no oil when diluted with water, the sodium salt of the aci-form of m-methoxy- $\alpha$ -hydroxy- $\omega$ -nitrostyrol (compare Bouveault and Wahl, Compt. Rend. 1902, 135, 141) was precipitated with ether, collected, and dehydrated by heating for 3 hours with fused zinc chloride (10g) and glacial acetic acid (50cc.). When this solution was mixed with water, the nitrostyrol separated in crystalline condition, and was collected, dried, and recrystallised from benzene-ligroin, from which it separated in shining yellow leaflets, m.p. 91-92° (Found: C, 60.3; H, 5.4.  $C_9H_9O_3N$  requires C, 60.3; H, 5.1%). It dissolved readily in chloroform, acetone, and hot benzene, but was insoluble in ligroin.

(ii) It was found that the method of Knoevenagel and Walter (Ber. 1904, 37, 4502), if followed exactly, resulted in what seemed to be an insoluble polymeride, and the following modification was therefore employed. A mixture of m-methoxybenzaldehyde (10.8g), nitromethane (5.2g), methylamine hydrochloride (0.4g), and anhydrous sodium carbonate (0.2g) in absolute alcohol (10cc.) was kept at room temperature during 48 hours. The shining plates which had separated were collected, washed with alcohol, and

found to be practically pure m-methoxy- $\omega$ -nitrostyrol. A small quantity of methylamine hydrochloride and sodium carbonate was added to the filtrate, and the mixture was left at room temperature for 24 hours. The crystals were collected, and successive crops were removed from the filtrate every 12 hours without further addition of the condensing reagents. When a total yield of 12g. had been isolated, a mixture of two substances began to separate from the solution. One of these was very sparingly soluble in the usual solvents, and seemed to be the polymeride mentioned above, while the other could be crystallised from alcohol. After several crystallisations from this solvent, it was obtained as pale yellow, non-lustrous clusters of needles, which melted at 91-92° and at the same temperature when mixed with the shining leaflets. It was thought at first that the two forms might be stereoisomeric, but a careful investigation of their crystalline forms and of the seeding of their solutions showed that they were merely dimorphic.

m-Methoxyphenylacetaldoxime. A mixture of the nitrostyrol (4g), zinc dust (10g), acetic acid (10g), and water (200cc.) was warmed on a water bath until most of the nitrostyrol had dissolved. A further quantity of zinc dust (5g)

was then added, and the heating continued for 20 minutes after all the styrol had dissolved. The liquid was boiled, filtered, and the filtrate deposited a brown oil, which showed signs of becoming crystalline. This was dissolved in ether, and the oxime was separated from the coloured impurities by repeated extraction of the ether with small quantities of sodium hydroxide. The alkaline solution was freed from ether and acidified with acetic acid. The colourless oil soon solidified and was collected, dried in vacuo, and crystallised from ligroin (b.p. 60-80°) (yield 0.4g or 11% of that theoretically possible). The oxime formed colourless needles, m.p. 91°, and was readily soluble in the usual solvents (Found: C, 65.6; H, 6.7.  $C_9H_{11}O_2N$  requires C, 65.5; H, 6.7%).

Formyl-m-methoxy-β-phenylethylamine. m-Methoxycinnamic acid was prepared in the manner which has since been described by Chakravarti, Haworth and Perkin (loc. cit.), and was converted into m-methoxy-β-phenylethylamine as described by Helfer (loc. cit.). The amine (20g.) and anhydrous formic acid (20g.) were heated in an oil bath at 175° for 6 hours, and the product was poured into water, extracted with benzene. The extract when dried and distilled yielded the formyl derivative as an oil, b.p. 216°/17mm. (Found: N, 7.9.  $C_{10}H_{13}O_2N$  requires N, 7.8%).



6-Methoxy-3:4-dihydroisoquinoline methiodide. The vigorous reaction which occurred when phosphorus oxychloride (25cc.) was added to formyl-m-methoxy- $\beta$ -phenylethylamine was moderated by cooling, and the mixture was then heated on the water bath for 2 hours, cooled, and mixed with ligroin. The basic product of the reaction, which remained as a salt in the lower layer, was washed with ligroin by decantation and dissolved in dilute hydrochloric acid. Concentrated potassium hydroxide solution precipitated from this acid solution the 6-methoxy-3:4-dihydroisoquinoline as an oil, which was extracted with benzene, and dried with solid potash. When methyl iodide was added to the dry, filtered solution, the methiodide (20g.) rapidly separated, and was recrystallised from alcohol, from which it separated in bright yellow needles, m.p. 199° (decomp.) (Found: I, 41.8.  $C_{11}H_{14}ONI$  requires I, 41.9%).

6-Methoxy-1-hydroxy-2-methyltetrahydroisoquinoline. The methiodide (5g.) was dissolved in warm water (50cc.), and the solution was cooled under the tap so that no separation of material occurred. Concentrated potassium hydroxide (15cc. of 50%) precipitated the pseudo-base as an oil, which rapidly crystallised when seeded with a crystal obtained previously by rubbing a small portion with ether. This product was collected at the pump on asbestos,



washed with a little water, and dried in vacuo over solid potash. When crystallised from benzene, the pseudo-base formed colourless prisms, m.p.  $102^{\circ}$ , which decomposed rather readily when dissolved in hot solvents (Found: N, 7.2.  $C_{11}H_{15}O_2N$  requires N, 7.2%).

6-Methoxy-1-keto-2-methyltetrahydroisoquinoline. The methiodide described above (6g.) dissolved in water (300cc.) was converted into the corresponding methochloride by the usual method. Dilute sodium hydroxide (60cc. of 2N) and potassium permanganate (1.1g. in 30cc. of water) were then added, and after 1 hour, the solution was filtered, neutralised with dilute sulphuric acid, and concentrated on the water bath. The oil which separated was dissolved in ether and dried with potassium carbonate. This extract yielded an oil which rapidly crystallised, and the quinolone separated from a mixture of ligroin (b.p.  $40-60^{\circ}$ ) and benzene in colourless rhombic plates, m.p.  $50^{\circ}$  (Found: C, 68.8; H, 6.7.  $C_{11}H_{13}O_2N$  requires C, 69.1; H, 6.8%).

Anhydrocotarnine-2-nitro-3:4-dimethoxybenzyl cyanide. A solution of cotarnine (1g.) and 2-nitro-3:4-dimethoxybenzyl cyanide (1g.) in alcohol (10cc.) was warmed for a few moments on the water bath until crystals formed in the liquid. When cold, the anhydro-compound was collected and

recrystallised from ethyl alcohol, forming colourless needles m.p.  $153^{\circ}$  (decomp.), having gradually become red from  $120^{\circ}$  (Found: C, 60.0, H, 5.4.  $C_{22}H_{23}O_7N_3$  requires C, 59.9; H, 5.2%).

Anhydrolaudaline-2-nitro-3:4-dimethoxybenzyl cyanide. A solution of laudaline (Pyman, J. 1909, 95, 1266; compare Robinson and Shinoda, J. 1926, 1989) (0.2g.) and 2-nitro-3:4-dimethoxybenzyl cyanide (0.2g.) in alcohol (6cc.) was warmed for a few minutes and allowed to remain overnight. Next day, the anhydro-derivative separated when the vessel was scratched with a glass rod, and was recrystallised from alcohol in clusters of faintly yellow needles, m.p.  $125-127^{\circ}$  (Found: C, 62.0; H, 6.1.  $C_{22}H_{25}O_6N_3$  requires C, 61.8; H, 5.9%).

2'-Nitro-3':4'-dimethoxyphenyl-1-(6-methoxy-2-methyltetrahydroisoquinoline) acetonitrile was prepared from 2-nitro-3:4-dimethoxybenzyl cyanide (4.8g.) and 6-methoxy-1-hydroxy-2-methyl tetrahydroisoquinoline (4.2g.) in a manner similar to that used in the preceding case. It crystallised from alcohol in clusters of yellow needles (6g.) which melted at  $95-96^{\circ}$ . (Found: C, 63.8; H, 5.8.  $C_{21}H_{23}O_5N_3$  requires C, 63.5; H, 5.8%).

Reduction of the Anhydro-base (IX). No reduction occurred when the base was treated with hot alcoholic ammonium sulphide, and the reduction was accordingly carried out in the following way. The base (2.1g.) in hot alcohol (60cc.) was added to a reducing mixture previously prepared by the addition of concentrated ammonia (20cc.) and hot alcohol (80cc.) to a solution of ferrous sulphate (12.5g.) in hot water (100cc.) containing a trace of sulphuric acid. This mixture was then heated on a water bath for 30 minutes, filtered, and the filtrate was mixed with about 400cc. of alcohol in order to precipitate all the ammonium sulphate. This was removed by filtration, and the alcohol evaporated under reduced pressure. The residual gum soon crystallised, and formed honey-coloured, boat-shaped plates, m.p.  $107^{\circ}$ , when recrystallised from water (Found: C, 62.5; H, 5.9; N, 14.5.  $C_{10}H_{12}O_2N_2$  requires C, 62.5; H, 6.2; N, 14.6%). The identity of this substance was determined by means of a mixed melting point determination with the specimen of 2-amino-3:4-dimethoxybenzyl cyanide described below.

2-Amino-3:4-dimethoxybenzyl cyanide. A solution of pure 2-nitro-3:4-dimethoxybenzyl cyanide (1g.) in hot alcohol (25cc.) was added to a reducing mixture of ferrous sulphate (11.2g.) in water (100cc.) and concentrated ammonia (20cc.). This mixture was heated on the water bath for

30 minutes, filtered through a thin layer of charcoal, and evaporated on the water bath until crystals separated on the surface of the liquid. The amino-nitrile separated completely on cooling, and was recrystallised from water, forming colourless needles, m.p. 108°. It dissolved in cold dilute hydrochloric acid, and the diazonium salts coupled with  $\beta$ -naphthol in alkaline solution. In attempting to hydrolyse this compound to form the corresponding oxindole (Publication 16), a solution in concentrated hydrochloric acid was boiled for 3 hours, poured into water, and rendered alkaline with ammonia. The solution at once became coloured, and rapidly passed through the series of green, purple, blue and black; no homogeneous material could be isolated.

The acetyl derivative was prepared by warming the base with acetic anhydride, adding water, and collecting the product. It crystallised from water in minute colourless needles, m.p. 184°, which were insoluble in dilute acids.

In order that the Bieckler-Sapieralski reaction for the preparation of isouquinoline bases might be applicable to the synthesis of aporphines in which the oxygen atoms of Ring I are in the 3:4-position, it was necessary to prepare large quantities of 2-nitro-3:4-dimethoxyphenylacetic acid (I).

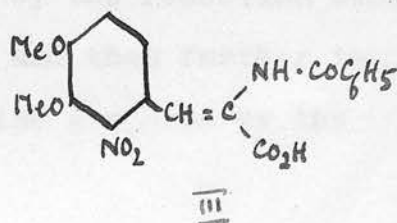
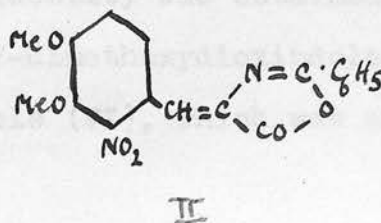
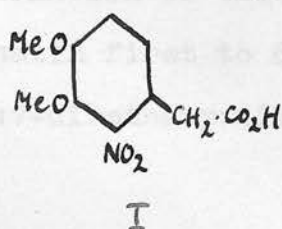
# PUBLICATION 16.

## NITRO-DERIVATIVES OF 3:4-DIHYDROXYPHENYLACETIC ACID.

103. 955; 104. 1007; 105. 1008; 106. 1009; 107. 1010; 108. 1011; 109. 1012; 110. 1013; 111. 1014; 112. 1015; 113. 1016; 114. 1017; 115. 1018; 116. 1019; 117. 1020; 118. 1021; 119. 1022; 120. 1023; 121. 1024; 122. 1025; 123. 1026; 124. 1027; 125. 1028; 126. 1029; 127. 1030; 128. 1031; 129. 1032; 130. 1033; 131. 1034; 132. 1035; 133. 1036; 134. 1037; 135. 1038; 136. 1039; 137. 1040; 138. 1041; 139. 1042; 140. 1043; 141. 1044; 142. 1045; 143. 1046; 144. 1047; 145. 1048; 146. 1049; 147. 1050; 148. 1051; 149. 1052; 150. 1053; 151. 1054; 152. 1055; 153. 1056; 154. 1057; 155. 1058; 156. 1059; 157. 1060; 158. 1061; 159. 1062; 160. 1063; 161. 1064; 162. 1065; 163. 1066; 164. 1067; 165. 1068; 166. 1069; 167. 1070; 168. 1071; 169. 1072; 170. 1073; 171. 1074; 172. 1075; 173. 1076; 174. 1077; 175. 1078; 176. 1079; 177. 1080; 178. 1081; 179. 1082; 180. 1083; 181. 1084; 182. 1085; 183. 1086; 184. 1087; 185. 1088; 186. 1089; 187. 1090; 188. 1091; 189. 1092; 190. 1093; 191. 1094; 192. 1095; 193. 1096; 194. 1097; 195. 1098; 196. 1099; 197. 1100; 198. 1101; 199. 1102; 200. 1103; 201. 1104; 202. 1105; 203. 1106; 204. 1107; 205. 1108; 206. 1109; 207. 1110; 208. 1111; 209. 1112; 210. 1113; 211. 1114; 212. 1115; 213. 1116; 214. 1117; 215. 1118; 216. 1119; 217. 1120; 218. 1121; 219. 1122; 220. 1123; 221. 1124; 222. 1125; 223. 1126; 224. 1127; 225. 1128; 226. 1129; 227. 1130; 228. 1131; 229. 1132; 230. 1133; 231. 1134; 232. 1135; 233. 1136; 234. 1137; 235. 1138; 236. 1139; 237. 1140; 238. 1141; 239. 1142; 240. 1143; 241. 1144; 242. 1145; 243. 1146; 244. 1147; 245. 1148; 246. 1149; 247. 1150; 248. 1151; 249. 1152; 250. 1153; 251. 1154; 252. 1155; 253. 1156; 254. 1157; 255. 1158; 256. 1159; 257. 1160; 258. 1161; 259. 1162; 260. 1163; 261. 1164; 262. 1165; 263. 1166; 264. 1167; 265. 1168; 266. 1169; 267. 1170; 268. 1171; 269. 1172; 270. 1173; 271. 1174; 272. 1175; 273. 1176; 274. 1177; 275. 1178; 276. 1179; 277. 1180; 278. 1181; 279. 1182; 280. 1183; 281. 1184; 282. 1185; 283. 1186; 284. 1187; 285. 1188; 286. 1189; 287. 1190; 288. 1191; 289. 1192; 290. 1193; 291. 1194; 292. 1195; 293. 1196; 294. 1197; 295. 1198; 296. 1199; 297. 1200; 298. 1201; 299. 1202; 300. 1203; 301. 1204; 302. 1205; 303. 1206; 304. 1207; 305. 1208; 306. 1209; 307. 1210; 308. 1211; 309. 1212; 310. 1213; 311. 1214; 312. 1215; 313. 1216; 314. 1217; 315. 1218; 316. 1219; 317. 1220; 318. 1221; 319. 1222; 320. 1223; 321. 1224; 322. 1225; 323. 1226; 324. 1227; 325. 1228; 326. 1229; 327. 1230; 328. 1231; 329. 1232; 330. 1233; 331. 1234; 332. 1235; 333. 1236; 334. 1237; 335. 1238; 336. 1239; 337. 1240; 338. 1241; 339. 1242; 340. 1243; 341. 1244; 342. 1245; 343. 1246; 344. 1247; 345. 1248; 346. 1249; 347. 1250; 348. 1251; 349. 1252; 350. 1253; 351. 1254; 352. 1255; 353. 1256; 354. 1257; 355. 1258; 356. 1259; 357. 1260; 358. 1261; 359. 1262; 360. 1263; 361. 1264; 362. 1265; 363. 1266; 364. 1267; 365. 1268; 366. 1269; 367. 1270; 368. 1271; 369. 1272; 370. 1273; 371. 1274; 372. 1275; 373. 1276; 374. 1277; 375. 1278; 376. 1279; 377. 1280; 378. 1281; 379. 1282; 380. 1283; 381. 1284; 382. 1285; 383. 1286; 384. 1287; 385. 1288; 386. 1289; 387. 1290; 388. 1291; 389. 1292; 390. 1293; 391. 1294; 392. 1295; 393. 1296; 394. 1297; 395. 1298; 396. 1299; 397. 1300; 398. 1301; 399. 1302; 400. 1303; 401. 1304; 402. 1305; 403. 1306; 404. 1307; 405. 1308; 406. 1309; 407. 1310; 408. 1311; 409. 1312; 410. 1313; 411. 1314; 412. 1315; 413. 1316; 414. 1317; 415. 1318; 416. 1319; 417. 1320; 418. 1321; 419. 1322; 420. 1323; 421. 1324; 422. 1325; 423. 1326; 424. 1327; 425. 1328; 426. 1329; 427. 1330; 428. 1331; 429. 1332; 430. 1333; 431. 1334; 432. 1335; 433. 1336; 434. 1337; 435. 1338; 436. 1339; 437. 1340; 438. 1341; 439. 1342; 440. 1343; 441. 1344; 442. 1345; 443. 1346; 444. 1347; 445. 1348; 446. 1349; 447. 1350; 448. 1351; 449. 1352; 450. 1353; 451. 1354; 452. 1355; 453. 1356; 454. 1357; 455. 1358; 456. 1359; 457. 1360; 458. 1361; 459. 1362; 460. 1363; 461. 1364; 462. 1365; 463. 1366; 464. 1367; 465. 1368; 466. 1369; 467. 1370; 468. 1371; 469. 1372; 470. 1373; 471. 1374; 472. 1375; 473. 1376; 474. 1377; 475. 1378; 476. 1379; 477. 1380; 478. 1381; 479. 1382; 480. 1383; 481. 1384; 482. 1385; 483. 1386; 484. 1387; 485. 1388; 486. 1389; 487. 1390; 488. 1391; 489. 1392; 490. 1393; 491. 1394; 492. 1395; 493. 1396; 494. 1397; 495. 1398; 496. 1399; 497. 1400; 498. 1401; 499. 1402; 500. 1403; 501. 1404; 502. 1405; 503. 1406; 504. 1407; 505. 1408; 506. 1409; 507. 1410; 508. 1411; 509. 1412; 510. 1413; 511. 1414; 512. 1415; 513. 1416; 514. 1417; 515. 1418; 516. 1419; 517. 1420; 518. 1421; 519. 1422; 520. 1423; 521. 1424; 522. 1425; 523. 1426; 524. 1427; 525. 1428; 526. 1429; 527. 1430; 528. 1431; 529. 1432; 530. 1433; 531. 1434; 532. 1435; 533. 1436; 534. 1437; 535. 1438; 536. 1439; 537. 1440; 538. 1441; 539. 1442; 540. 1443; 541. 1444; 542. 1445; 543. 1446; 544. 1447; 545. 1448; 546. 1449; 547. 1450; 548. 1451; 549. 1452; 550. 1453; 551. 1454; 552. 1455; 553. 1456; 554. 1457; 555. 1458; 556. 1459; 557. 1460; 558. 1461; 559. 1462; 560. 1463; 561. 1464; 562. 1465; 563. 1466; 564. 1467; 565. 1468; 566. 1469; 567. 1470; 568. 1471; 569. 1472; 570. 1473; 571. 1474; 572. 1475; 573. 1476; 574. 1477; 575. 1478; 576. 1479; 577. 1480; 578. 1481; 579. 1482; 580. 1483; 581. 1484; 582. 1485; 583. 1486; 584. 1487; 585. 1488; 586. 1489; 587. 1490; 588. 1491; 589. 1492; 590. 1493; 591. 1494; 592. 1495; 593. 1496; 594. 1497; 595. 1498; 596. 1499; 597. 1500; 598. 1501; 599. 1502; 600. 1503; 601. 1504; 602. 1505; 603. 1506; 604. 1507; 605. 1508; 606. 1509; 607. 1510; 608. 1511; 609. 1512; 610. 1513; 611. 1514; 612. 1515; 613. 1516; 614. 1517; 615. 1518; 616. 1519; 617. 1520; 618. 1521; 619. 1522; 620. 1523; 621. 1524; 622. 1525; 623. 1526; 624. 1527; 625. 1528; 626. 1529; 627. 1530; 628. 1531; 629. 1532; 630. 1533; 631. 1534; 632. 1535; 633. 1536; 634. 1537; 635. 1538; 636. 1539; 637. 1540; 638. 1541; 639. 1542; 640. 1543; 641. 1544; 642. 1545; 643. 1546; 644. 1547; 645. 1548; 646. 1549; 647. 1550; 648. 1551; 649. 1552; 650. 1553; 651. 1554; 652. 1555; 653. 1556; 654. 1557; 655. 1558; 656. 1559; 657. 1560; 658. 1561; 659. 1562; 660. 1563; 661. 1564; 662. 1565; 663. 1566; 664. 1567; 665. 1568; 666. 1569; 667. 1570; 668. 1571; 669. 1572; 670. 1573; 671. 1574; 672. 1575; 673. 1576; 674. 1577; 675. 1578; 676. 1579; 677. 1580; 678. 1581; 679. 1582; 680. 1583; 681. 1584; 682. 1585; 683. 1586; 684. 1587; 685. 1588; 686. 1589; 687. 1590; 688. 1591; 689. 1592; 690. 1593; 691. 1594; 692. 1595; 693. 1596; 694. 1597; 695. 1598; 696. 1599; 697. 1600; 698. 1601; 699. 1602; 700. 1603; 701. 1604; 702. 1605; 703. 1606; 704. 1607; 705. 1608; 706. 1609; 707. 1610; 708. 1611; 709. 1612; 710. 1613; 711. 1614; 712. 1615; 713. 1616; 714. 1617; 715. 1618; 716. 1619; 717. 1620; 718. 1621; 719. 1622; 720. 1623; 721. 1624; 722. 1625; 723. 1626; 724. 1627; 725. 1628; 726. 1629; 727. 1630; 728. 1631; 729. 1632; 730. 1633; 731. 1634; 732. 1635; 733. 1636; 734. 1637; 735. 1638; 736. 1639; 737. 1640; 738. 1641; 739. 1642; 740. 1643; 741. 1644; 742. 1645; 743. 1646; 744. 1647; 745. 1648; 746. 1649; 747. 1650; 748. 1651; 749. 1652; 750. 1653; 751. 1654; 752. 1655; 753. 1656; 754. 1657; 755. 1658; 756. 1659; 757. 1660; 758. 1661; 759. 1662; 760. 1663; 761. 1664; 762. 1665; 763. 1666; 764. 1667; 765. 1668; 766. 1669; 767. 1670; 768. 1671; 769. 1672; 770. 1673; 771. 1674; 772. 1675; 773. 1676; 774. 1677; 775. 1678; 776. 1679; 777. 1680; 778. 1681; 779. 1682; 780. 1683; 781. 1684; 782. 1685; 783. 1686; 784. 1687; 785. 1688; 786. 1689; 787. 1690; 788. 1691; 789. 1692; 790. 1693; 791. 1694; 792. 1695; 793. 1696; 794. 1697; 795. 1698; 796. 1699; 797. 1700; 798. 1701; 799. 1702; 800. 1703; 801. 1704; 802. 1705; 803. 1706; 804. 1707; 805. 1708; 806. 1709; 807. 1710; 808. 1711; 809. 1712; 810. 1713; 811. 1714; 812. 1715; 813. 1716; 814. 1717; 815. 1718; 816. 1719; 817. 1720; 818. 1721; 819. 1722; 820. 1723; 821. 1724; 822. 1725; 823. 1726; 824. 1727; 825. 1728; 826. 1729; 827. 1730; 828. 1731; 829. 1732; 830. 1733; 831. 1734; 832. 1735; 833. 1736; 834. 1737; 835. 1738; 836. 1739; 837. 1740; 838. 1741; 839. 1742; 840. 1743; 841. 1744; 842. 1745; 843. 1746; 844. 1747; 845. 1748; 846. 1749; 847. 1750; 848. 1751; 849. 1752; 850. 1753; 851. 1754; 852. 1755; 853. 1756; 854. 1757; 855. 1758; 856. 1759; 857. 1760; 858. 1761; 859. 1762; 860. 1763; 861. 1764; 862. 1765; 863. 1766; 864. 1767; 865. 1768; 866. 1769; 867. 1770; 868. 1771; 869. 1772; 870. 1773; 871. 1774; 872. 1775; 873. 1776; 874. 1777; 875. 1778; 876. 1779; 877. 1780; 878. 1781; 879. 1782; 880. 1783; 881. 1784; 882. 1785; 883. 1786; 884. 1787; 885. 1788; 886. 1789; 887. 1790; 888. 1791; 889. 1792; 890. 1793; 891. 1794; 892. 1795; 893. 1796; 894. 1797; 895. 1798; 896. 1799; 897. 1800; 898. 1801; 899. 1802; 900. 1803; 901. 1804; 902. 1805; 903. 1806; 904. 1807; 905. 1808; 906. 1809; 907. 1810; 908. 1811; 909. 1812; 910. 1813; 911. 1814; 912. 1815; 913. 1816; 914. 1817; 915. 1818; 916. 1819; 917. 1820; 918. 1821; 919. 1822; 920. 1823; 921. 1824; 922. 1825; 923. 1826; 924. 1827; 925. 1828; 926. 1829; 927. 1830; 928. 1831; 929. 1832; 930. 1833; 931. 1834; 932. 1835; 933. 1836; 934. 1837; 935. 1838; 936. 1839; 937. 1840; 938. 1841; 939. 1842; 940. 1843; 941. 1844; 942. 1845; 943. 1846; 944. 1847; 945. 1848; 946. 1849; 947. 1850; 948. 1851; 949. 1852; 950. 1853; 951. 1854; 952. 1855; 953. 1856; 954. 1857; 955. 1858; 956. 1859; 957. 1860; 958. 1861; 959. 1862; 960. 1863; 961. 1864; 962. 1865; 963. 1866; 964. 1867; 965. 1868; 966. 1869; 967. 1870; 968. 1871; 969. 1872; 970. 1873; 971. 1874; 972. 1875; 973. 1876; 974. 1877; 975. 1878; 976. 1879; 977. 1880; 978. 1881; 979. 1882; 980. 1883; 981. 1884; 982. 1885; 983. 1886; 984. 1887; 985. 1888; 986. 1889; 987. 1890; 988. 1891; 989. 1892; 990. 1893; 991. 1894; 992. 1895; 993. 1896; 994. 1897; 995. 1898; 996. 1899; 997. 1900; 998. 1901; 999. 1902; 1000. 1903; 1001. 1904; 1002. 1905; 1003. 1906; 1004. 1907; 1005. 1908; 1006. 1909; 1007. 1910; 1008. 1911; 1009. 1912; 1010. 1913; 1011. 1914; 1012. 1915; 1013. 1916; 1014. 1917; 1015. 1918; 1016. 1919; 1017. 1920; 1018. 1921; 1019. 1922; 1020. 1923; 1021. 1924; 1022. 1925; 1023. 1926; 1024. 1927; 1025. 1928; 1026. 1929; 1027. 1930; 1028. 1931; 1029. 1932; 1030. 1933; 1031. 1934; 1032. 1935; 1033. 1936; 1034. 1937; 1035. 1938; 1036. 1939; 1037. 1940; 1038. 1941; 1039. 1942; 1040. 1943; 1041. 1944; 1042. 1945; 1043. 1946; 1044. 1947; 1045. 1948; 1046. 1949; 1047. 1950; 1048. 1951; 1049. 1952; 1050. 1953; 1051. 1954; 1052. 1955; 1053. 1956; 1054. 1957; 1055. 1958; 1056. 1959; 1057. 1960; 1058. 1961; 1059. 1962; 1060. 1963; 1061. 1964; 1062. 1965; 1063. 1966; 1064. 1967; 1065. 1968; 1066. 1969; 1067. 1970; 1068. 1971; 1069. 1972; 1070. 1973; 1071. 1974; 1072. 1975; 1073. 1976; 1074. 1977; 1075. 1978; 1076. 1979; 1077. 1980; 1078. 1981; 1079. 1982; 1080. 1983; 1081. 1984; 1082. 1985; 1083. 1986; 1084. 1987; 1085. 1988; 1086. 1989; 1087. 1990; 1088. 1991; 1089. 1992; 1090. 1993; 1091. 1994; 1092. 1995; 1093. 1996; 1094. 1997; 1095. 1998; 1096. 1999; 1097. 2000; 1098. 2001; 1099. 2002; 1100. 2003; 1101. 2004; 1102. 2005; 1103. 2006; 1104. 2007; 1105. 2008; 1106. 2009; 1107. 2010; 1108. 2011; 1109. 2012; 1110. 2013; 1111. 2014; 1112. 2015; 1113. 2016; 1114. 2017; 1115. 2018; 1116. 2019; 1117. 2020; 1118. 2021; 1119. 2022; 1120. 2023; 1121. 2024; 1122. 2025; 1123. 2026; 1124. 2027; 1125. 2028; 1126. 2029; 1127. 2030; 1128. 2031; 1129. 2032; 1130. 2033; 1131. 2034; 1132. 2035; 1133. 2036; 1134. 2037; 1135. 2038; 1136. 2039; 1137. 2040; 1138. 2041; 1139. 2042; 1140. 2043; 1141. 2044; 1142. 2045; 1143. 2046; 1144. 2047; 1145. 2048; 1146. 2049; 1147. 2050; 1148. 2051; 1149. 2052; 1150. 2053; 1151. 2054; 1152. 2055; 1153. 2056; 1154. 2057; 1155. 2058; 1156. 2059; 1157. 2060; 1158. 2061; 1159. 2062; 1160. 2063; 1161. 2064; 1162. 2065; 1163. 2066; 1164. 2067; 1165. 2068; 1166. 2069; 1167. 2070; 1168. 2071; 1169. 2072; 1170. 2073; 1171. 2074; 1172. 2075; 1173. 2076; 1174. 2077; 1175. 2078; 1176. 2079; 1177. 2080; 1178. 2081; 1179. 2082; 1180. 2083; 1181. 2084; 1182. 2085; 1183. 2086; 1184. 2087; 1185. 2088; 1186. 2089; 1187.



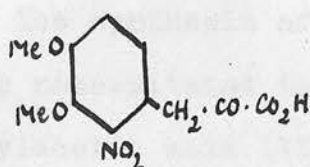
In order that the Bischler-Napieralski reaction for the preparation of isoquinoline bases might be applicable to the synthesis of aporphines in which the oxygen atoms of Ring I are in the 3:4-positions, it became necessary to prepare large quantities of 2-nitro-3:4-dimethoxyphenylacetic acid (I). This acid had already been obtained by Kay and Pictet (J. 1913. 103. 950), but only by a long series of processes of which one was a Cannizzaro reaction where the desired product was the alcohol, and it was therefore highly important to explore less tedious methods of preparing the acid in better yield than that recorded by the earlier investigators. The smooth decomposition of  $\alpha$ -ketonic acids into carbon dioxide and carboxylic acids containing -CO- less than the parent substance, by oxidation with hydrogen peroxide in alkaline solution, seemed to offer a possible route to this end, more especially as the method which it was decided to employ had been used with marked success by other workers for the preparation of phenylacetic acids (Mauthner, Ann. 1909. 370. 368; Kropp and Decker, Ber. 1909. 42. 1184; Cain, Simonsen, and Smith, J. 1913. 103. 1036). There was no record of the formation of a nitrophenylacetic acid in this way, but the early stages proceeded smoothly in the expected manner. The azlactone (II) was readily obtained by the condensation of



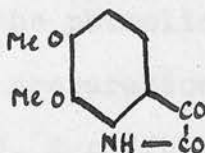
2-nitroveratraldehyde (Pschorr and Sumuleanu, Ber. 1899. 32. 3405; Pschorr and Stöhrer, Ber. 1902. 35. 4397; Pisovschi, Ber. 1910. 43. 2137) with hippuric acid, and the hydrolysis of this with hot alcoholic hydrochloric acid or with dilute sodium hydroxide for a short time yielded 2-nitro-3:4-dimethoxy- $\alpha$ -benzoylaminocinnamic acid (III). When the alkaline hydrolysis was prolonged, abnormal results were obtained, and none of the expected phenylpyruvic acid (IV) could be isolated. In addition to ammonia, benzoic acid, carbon dioxide and oxalic acid, the products of the reaction were a nitrogenous ketone  $C_{10}H_9O_4N$ , and an aromatic amino-acid  $C_9H_{11}O_4N$ . This acid contained a primary amino-group which could be diazotised and acetylated, and the identity of the substance as 2-aminoveratric acid (Kühn, Ber. 1895. 28. 810, Pschorr and Sumuleanu, loc.cit.) was determined by a mixed melting point, and by the melting point of the acetyl-derivative.

The properties of the ketone were reminiscent of those of isatin, and the conclusion that the substance was 6:7-dimethoxyisatin (V) was strongly supported by the preparation of a semicarbazone, and by the indophenine reaction which the ketone exhibited with thiophene and sulphuric acid. Complete confirmation of this identity was obtained by the reduction of the isatin first to 6:7-dimethoxydioxindole and then further to 6:7-dimethoxyoxindole (VI), which was also prepared by the

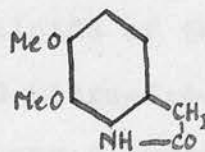
reduction of 2-nitro-3:4-dimethoxyphenylacetic acid.



IV



V



VI

The course taken by this reaction is clearly yet another instance of the internal oxidation and reduction which occurs in compounds where a nitro-group is in the ortho-position to a carbon chain. Examples of these changes are the well-known conversion of an o-nitroaldehyde to the corresponding nitroso-acid (Ciamician and Silber, Ber. 1901. 34. 2040); the transformation of o-nitrotoluene by boiling alkali first into anthranil, and then into anthranilic acid (Preuss and Binz, Z. für angew. Chem. 1900, 385; Bamberger, Ber. 1903. 36. 836; and the formation of isatin from o-nitrophenylpropionic acid (Baeyer Ber. 1880. 13. 2254). The small quantity of amino-veratric acid which is also produced is probably due to further oxidation or hydrolysis at the  $\alpha$ -carbon atom of the side chain.

These methods were obviously unsuitable for the preparation of 2-nitro-3:4-dimethoxyphenylacetic acid, and no alternative remained but to modify the methods of Kay and Pictet so that they might be available for the treatment of large quantities

of material. The details of these modifications are described in the experimental part of the paper.

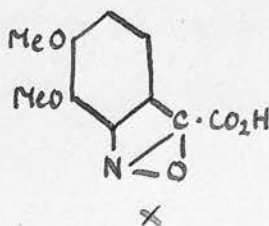
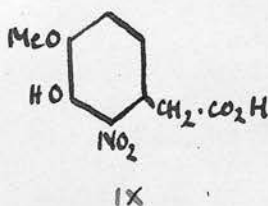
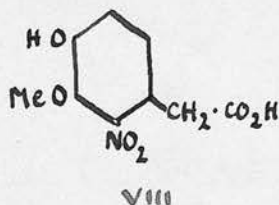
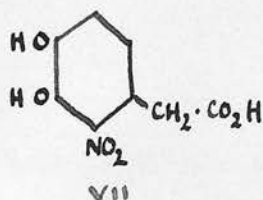
The synthesis of the phenolic alkaloids of the corytuberine group necessitated the preparation of 2-nitro-3:4-dihydroxyphenylacetic acid (VII), 2-nitro-3-methoxy-4-hydroxyphenylacetic acid (VIII), and the isomeric 2-nitro-4-methoxy-3-hydroxyphenylacetic acid (IX), and with this object in view a study was made of the demethylation of 2-nitro-3:4-dimethoxyphenylacetic acid. This reaction, simple though it may seem, has proved exceedingly difficult to control, but conditions have been defined by which the acids (VII) and (VIII) may be obtained simultaneously by demethylation with boiling hydrobromic acid.

The protection of the hydroxyl groups of these acids during the early stages of the aporphine synthesis is a matter of considerable importance, and the carbethoxy- and benzyloxy-derivatives have been prepared, and tested as regards their stability to hydrolytic reagents. The protective groups of both classes are rapidly removed by hot, moderately concentrated hydrochloric acid (as in the reduction of the nitrobenzylisoquinolines), but in less concentrated acid, the carbethoxylated acids exhibit greater stability than the benzyloxy-derivatives. Further, the normal benzylation of the phenolic acid is a side-reaction only of the action of benzyl



chloride on the sodium salt, and the greater part of the product is a benzyl-ester, which has also undergone a more deep-seated change. Carbethoxylation proceeded very smoothly on the other hand, and the carbethoxy-group was therefore selected for protective purposes.

Partial demethylation (at position 3) of 2-nitro-3:4-dimethoxyphenylacetic acid cannot be effected by means of boiling sodium hydroxide solution, because a process of internal oxidation and reduction occurs, and the product is 5:6-dimethoxyanthranilcarboxylic acid (X). The alternative method which is available for the preparation of the acid (IX), namely partial methylation of 2-nitro-3:4-dihydroxyphenylacetic acid, has not yet been investigated thoroughly, but it seems that this step will prove difficult, since no methylation takes place at cold temperatures, and on warming, both hydroxyl groups are etherified.





6-Nitro-3:4-dimethoxyphenylacetic acid was required for the synthesis of Gorter's isoglaucine, and this was prepared by the nitration of 3:4-dimethoxyphenylacetic acid. This method is more convenient than that described by Oxford and Raper (J. 1927, 417).

3:4-Dimethoxyphenylacetic acid (12g) which had previously been heated to 100° on the water bath, in a few minutes the colour of the liquid became red, and after 15 minutes the product separated in crystalline form. Alcohol (20cc) was added, the solution was cooled, and the solid was filtered off. The solid was washed with 20% alcohol. The solid was dried in a vacuum desiccator. The solid was 1.2g, m.p. 145° (decolor). The solid was not improved by prolonged heating during the reaction.

The solid was crystallized from ethyl acetate in yellow, foliated needles, m.p. 145-146° (decolor).  $C_{10}H_9NO_5$ : Calcd. C, 58.4%; H, 4.3%; N, 3.3%. Found: C, 58.1%; H, 4.3%; N, 3.3%. The solid was recrystallized from ethyl acetate and gave a melting point of 145° (decolor). (J. 1927, 417).

6-Nitro-3:4-dimethoxyphenylacetic acid. This compound was prepared by the nitration of 3:4-dimethoxyphenylacetic acid. The solid was 1.2g, m.p. 145° (decolor). The solid was not improved by prolonged heating during the reaction. The solid was crystallized from ethyl acetate in yellow, foliated needles, m.p. 145-146° (decolor).  $C_{10}H_9NO_5$ : Calcd. C, 58.4%; H, 4.3%; N, 3.3%. Found: C, 58.1%; H, 4.3%; N, 3.3%. The solid was recrystallized from ethyl acetate and gave a melting point of 145° (decolor). (J. 1927, 417).

# EXPERIMENTAL.

Anhydride of 2-nitro-3:4-dimethoxy- $\alpha$ -benzoylaminocinnamic acid. Powdered anhydrous sodium acetate (12g) was added to a mixture of 2-nitroveratraldehyde (12g), hippuric acid (11g), and acetic anhydride (20cc.) which had previously been heated to 100° on the water bath. In a few minutes the colour of the liquid became deep red, heat was evolved, and soon the product separated in crystalline form. Alcohol (20cc. of 70%) <sup>was</sup> ~~were~~ then added, the solution was cooled, and the azlactone collected, washed with 70% alcohol until colourless, and then treated repeatedly with boiling water. The yield was 14g., and this was not improved by prolonged heating during the reaction.

The azlactone crystallised from alcohol or from ethyl acetate in yellow, felted needles, m.p. 169-170° (Found: C, 60.5; H, 4.3; N, 7.7. Calc. for  $C_{18}H_{14}O_6N_2$ , C, 61.0; H, 3.9; N, 7.9%). Bain, Perkin and Robinson give the melting point as 145° (J. 1914. 105. 2403).

2-Nitro-3:4-dimethoxy- $\alpha$ -benzoylaminocinnamic acid. Hydrolysis of the azlactone was readily carried out by heating with 10% aqueous sodium hydroxide solution, or by means of boiling aqueous alcoholic hydrochloric acid. On acidifying the solution in the first case, or by cooling in the second case, the acid was obtained in crystalline form, and was crystallised

from 70% alcohol. It formed colourless needles, m.p.  $216-217^{\circ}$  (Found in material dried at  $100^{\circ}$ : C, 58.1; H, 4.3. Calc. for  $C_{18}H_{16}O_7N_2$  C, 58.1; H, 4.3%). The acid was readily soluble in alcohol acetone, and acetic acid, but dissolved sparingly in benzene, ether, and chloroform. The azlactone was regenerated by heating with acetic anhydride.

Prolonged Alkaline Hydrolysis of the Azlactone. A solution of the azlactone (8g) and sodium hydroxide (4.8g) in water (40cc.) and alcohol (120cc.) was boiled under reflux for  $5\frac{1}{2}$  hours, cooled and separated by filtration from sodium carbonate (3.6g). After the alcohol had been evaporated away, excess of sulphur dioxide was passed into the solution, and the precipitate (A) collected, washed with water, and dried in a desiccator. The filtrate was mixed with excess of hydrochloric acid, boiled to expel sulphur dioxide, cooled, and extracted repeatedly with chloroform. The extracts were dried with sodium sulphate and distilled, leaving a mass of dark red needles (B). The fraction A was separated by crystallisation from benzene into a readily soluble portion, which was later identified as benzoic acid, and a sparingly soluble portion (C).

Fraction B. 6:7-Dimethoxyisatin . (1.2g.). This was crystallised twice from alcohol and then formed orange needles, m.p.  $210^{\circ}$

(Found: C, 58.1; H, 4.5; N, 6.6.  $C_{10}H_9O_4N$  requires C, 58.0; H, 4.3 N, 6.8%). This substance was readily soluble in acetone and chloroform, but sparingly soluble in benzene and ether. It did not dissolve in cold sodium carbonate, but with sodium hydroxide it formed a crimson solution which rapidly became yellow. An orange colour was developed with concentrated sulphuric acid, and with thiophene and sulphuric acid, a green-blue indophenine was formed.

Dimethoxyisatin semicarbazone was prepared by warming for 5 minutes on the water bath a mixture of the ketone (1.5g), semicarbazide hydrochloride (0.81g), excess of sodium acetate, and alcohol (15cc.), cooling, and adding water. The precipitate was collected and crystallised from alcohol in small yellow needles, m.p.  $254^{\circ}$  (decomp.), or from dilute acetic acid in yellow needles m.p.  $250^{\circ}$  unsharply. These are anhydrous, whereas those from alcohol contained one molecule of water of crystallisation. (Found in material from alcohol: N, 20.1.  $C_{11}H_{12}O_4N_4 \cdot H_2O$  requires N, 19.8. Found in material from dilute acetic acid: N, 21.0;  $C_{11}H_{12}O_4N_4$  requires N, 21.2%). This substance dissolved in sodium hydroxide forming an orange solution, and was sparingly soluble in the usual solvents.

Fraction C. 2-Aminoveratric acid (1.0g). This was crystallised from water and from benzene, and formed colourless needles, m.p.

182-183° (Found: C, 54.9; H, 5.6.  $C_9H_{11}O_4N$  requires C, 54.8; H, 5.6%). The presence of a primary aromatic amino-group was shown by coupling the diazonium salt with  $\beta$ -naphthol, and the acetyl-derivative melted at 190°. These properties were those of 2-aminoveratric acid, and the identity of the substance was confirmed by a mixed melting point with an authentic specimen.

6:7-Dimethoxydioxindole. A boiling solution of the isatin (3.4g) in water (150cc.) was mixed with sodium hydrosulphite (10g), filtered, and cooled. The product separated from the pale yellow liquid, and was recrystallised from water in leaflets m.p. 200° (Found: C, 57.4; H, 5.4.  $C_{10}H_{11}O_4N$  requires C, 57.4; H, 5.3%).

6:7-Dimethoxyoxindole. A fine suspension of the dioxindole (2g), alcohol (10cc.), water (45cc.) and sodium bicarbonate (0.5g) was saturated with carbon dioxide while cooled in ice, and reduced by the gradual addition of 4% sodium amalgam (35g). Next day the precipitate was collected and extracted with ether; the solvent was distilled, and the residue crystallised from water. Dimethoxyoxindole formed almost colourless needles m.p. 192-193° which were readily soluble in ether and alcohol (Found: C, 62.3; H, 5.8.  $C_{10}H_{11}O_3N$



requires C, 62.2; H, 5.7%). It was identical with the specimen prepared as described below.

2-Amino-3:4-dimethoxyphenylacetic acid. A solution of 2-nitro-3:4-dimethoxyphenylacetic acid (1g) in hot dilute ammonia (30cc.) was added to a hot reducing mixture of ferrous sulphate (10.5g) in water (100cc.) and concentrated ammonia (10cc.). The mixture was heated for 30 minutes, filtered, and the filtrate evaporated in an open basin to a volume of 40cc. (It is essential that the solution should not be allowed to evaporate to dryness, as dehydration takes place, and the product is then a mixture of the amino-acid and the oxindole). Several extractions with ether removed the whole of the product, which was then isolated by distilling the ether. The amino-acid crystallised from water in almost colourless needles, m.p.  $154^{\circ}$ . (Found in material dried at  $100^{\circ}$  for 15 minutes: C, 57.0; H, 6.1.  $\text{C}_{10}\text{H}_{13}\text{O}_4\text{N}$  requires C, 56.9; H, 6.1%). It dissolved in cold bicarbonate solution, and when diazotised coupled with  $\beta$ -naphthol in alkaline solution. When heated at  $160^{\circ}$  in an oil bath, it effervesced, and the residue immediately crystallised in needles. This proved to be 6:7-dimethoxyoxindole, which crystallised from water in needles, and melted at  $193^{\circ}$  and at the same temperature when mixed with

the specimen prepared as described above.

2-Nitro-3:4-dimethoxyphenylacetic acid. Vanillin (600g) was converted into 2-nitroveratraldehyde (380g) as described by Pisovschi, (loc. cit.) by the processes of acetylation, nitration, hydrolysis, and methylation. This 2-nitroveratraldehyde was subjected in four batches to the action of alcoholic potash (equal weights of aldehyde, potassium hydroxide, alcohol, and water) as described by Kay and Pictet. The mixture was poured into water, and extracted thoroughly with benzene. After being washed thoroughly with sodium bisulphite solution, the extract was dried with sodium sulphate, and the benzene removed by distillation under slightly reduced pressure. The residual 2-nitro-3:4-dimethoxybenzyl alcohol (150g), which was practically pure and crystallised on cooling, was dissolved in chloroform (1500cc.), cooled in ice, and converted into 2-nitroveratryl chloride by the gradual addition of phosphorus pentachloride (150g). After some hours the mixture was poured into water, and next day the chloroform layer was separated, dried with sodium sulphate, and distilled; the pressure was reduced at the end of the distillation in order to remove all the solvent and phosphorus oxychloride. The residual 2-nitroveratrylchloride crystallised immediately (160g), and was dissolved in alcohol (700cc.), mixed with potassium cyanide (90g) in water (170cc.), and heated on the

water bath under reflux for about 7 hours. The residue was then poured into water (2.5 litres) and 2-nitro-3:4-dimethoxy-benzyl cyanide was collected and dried in a vacuum desiccator. This dark-coloured crude material (135g) was dissolved in ether as far as possible, and the ethereal solution was dried with sodium sulphate and saturated with dry hydrogen chloride while being cooled in ice. Next day, the imino-ether hydrochloride was collected and converted into 2-nitro-3:4-dimethoxyphenylacetic acid in the manner described by Kay and Pictet. The yield was 100gms.

For the purposes of those experiments in which 2-nitro-3:4-dimethoxybenzyl cyanide was required in pure condition, the crude preparation was recrystallised from methyl alcohol, one purification in this way being sufficient.

2-Nitro-3:4-dimethoxyphenylacetamide was isolated from the aqueous alcoholic filtrate from the preparation of the nitrile by extraction with chloroform. The extract was dried and distilled, and the residual oil crystallised when rubbed with methyl alcohol. The amide crystallised from this solvent in colourless needles, m.p.  $153^{\circ}$  (Found: N, 11.7%.  $C_{10}H_{12}O_5N_2$  requires N, 11.7%). The acid is formed by hydrolysis with alkali.

The Demethylation of 2-Nitro-3:4-dimethoxyphenylacetic Acid.

The yields in this process depend on the intensity and

duration of heating, and the following description is typical.

A mixture of the acid (10g) and concentrated hydrobromic acid (70cc. of 47.5%) was raised rapidly to the boiling point by heating over a free flame, and the solution was maintained for 15 minutes at such a temperature that gentle ebullition occurred. The dark red solution was cooled, and after 2 hours 2-nitro-3-methoxy-4-hydroxyphenylacetic acid was collected, washed with hydrobromic acid and then with water, and crystallised from water (yield, 2.2g).

The filtrate from this reaction contained 2-nitro-3:4-dihydroxyphenylacetic acid, which was isolated by diluting with water, (200cc.), filtering from a little amorphous material, and extracting repeatedly with ethyl acetate. The extracts were dried with sodium sulphate, and the ethyl acetate was removed by distillation, reduced pressure being employed finally to remove acetic acid as far as possible. The residual red oil solidified, and after being rubbed with benzene in which it was insoluble, the crystals of 2-nitro-3:4-dimethoxyphenylacetic acid were collected (5.5g).

2-Nitro-3-methoxy-4-hydroxyphenylacetic acid formed orange yellow needles when crystallised from water and shining orange leaflets when crystallised from toluene; both specimens melted at  $161^{\circ}$  (Found: C, 47.6; H, 3.9.  $C_9H_9O_6N$  requires C, 47.6;



H, 3.9%). This acid dissolved readily in alcohol, formed an orange solution in sodium hydroxide, and developed a feeble green colour with alcoholic ferric chloride.

2-Nitro-3-methoxy-4-carbethoxyphenylacetic acid. The phenolic acid (10g) dissolved in water (30cc.) and dilute sodium hydroxide (50cc. of 10%) was cooled in ice and shaken with chloroformic ester (10g. added in two batches). The solution remained alkaline, and the red colour was discharged in the course of a few minutes. Excess of dilute hydrochloric acid was added, the liberated oil was taken up in ether, and the ethereal extract shaken repeatedly with small quantities of potassium bicarbonate solution. Acidification of this solution yielded the desired acid as an oil which rapidly crystallised; it was collected and dried on porous tile (11.4g), and recrystallised from benzene by dissolving in the solvent (charcoal), filtering, and concentrating until crystals began to separate. 2-Nitro-3-methoxy-4-carbethoxyphenylacetic acid formed colourless diamond-shaped tablets, which melted at 110-118° while losing solvent of crystallisation, and at 132-133° after being heated at 110° (Loss at 110°: 11.7.  $C_{12}H_{13}O_8N$ .  $\frac{1}{2}C_6H_6$  requires 11.5%. Found: C.48.1; H.4.3.  $C_{12}H_{13}O_8N$  requires C, 48.1; H, 4.3%) It was rather readily soluble in the usual solvents, and dissolved in 2N sodium carbonate to form a colourless solution. The carbethoxy-group was instantly hydrolysed by cold 2N sodium hydroxide, but the acid



was not affected by heating at  $100^{\circ}$  for 20 minutes in 2N hydrochloric acid.

The ethereal extract from the preceding preparation contained a pale-pink, uncrystallisable oil which was obtained by distilling the ether and stirring the residue with ligroin so as to dissolve the excess of chloroformic ester. This oil, which may have been ethyl 2-nitro-3-methoxy-4-carbethoxy-phenylacetate, produced by the introduction of the carbethoxy-group at the reactive methylene-group and elimination of the carboxyl of the acid, was converted into the original phenolic acid by heating with dilute alcoholic potash on the water bath for a few minutes and acidifying with hydrochloric acid. Ethyl acetate extracted the acid, which was obtained by distillation of the solvent, and was crystallised from water (yield, 0.6g).

Benzylation of 2-Nitro-3-methoxy-4-<sup>hydr</sup>~~carbeth~~oxyphenylacetic acid.

No benzylation occurred when the acid was heated with benzyl chloride and powdered potassium carbonate in dry acetone, and the following procedure was therefore adopted. A solution of the phenolic acid (1g) in sodium carbonate (30cc. of 2N) was boiled under reflux for about 1 hour until the red colour was discharged. The liquid was cooled, extracted with ether to remove the excess of benzyl chloride (see below), and acidified. The oily benzylated acid, which soon crystallised, was dissolved in hot benzene, and the solution concentrated. The crystals

(0.4g) which separated on cooling were recrystallised from benzene; the benzylated acid formed colourless hexagonal plates, m.p.  $108-109^{\circ}$  (Found: C, 60.8; H, 4.9.  $\text{C}_{16}\text{H}_{15}\text{O}_6\text{N}$  requires C, 60.6; H, 4.7%). It formed a colourless solution in sodium hydroxide solution, and was stable to boiling alkali, but the benzyl-group was hydrolysed by heating for a few moments with dilute hydrochloric acid.

The ethereal extract from the preparation contained the by-product, which was obtained in crystalline condition by evaporating the ether, and stirring the residual oil with ligroin to dissolve the benzyl chloride. The yield was 0.64g. One crystallisation from ligroin (b.p.  $60-80^{\circ}$ ) containing a few drops of benzene yielded this substance as colourless needles, m.p.  $80^{\circ}$ , which were insoluble in acid and alkali. (Found: C, 66.4; H, 3.3; N, 5.0%). It is clear from these analytical figures that two benzyl groups have been introduced into the molecule. This substance was not affected by heating for 10 minutes with dilute hydrochloric acid, but dissolved slowly in boiling sodium hydroxide yielding an acid which was precipitated by acidification. This acid crystallised from dilute alcohol in colourless needles, m.p.  $144^{\circ}$ , which formed a colourless solution in sodium carbonate.

2-Nitro-3:4-dihydroxyphenylacetic acid, when crystallised from xylene, formed orange yellow needles, m.p.  $171^{\circ}$ , which were

readily soluble in water and in alcohol, and developed an intense blue-green colour with alcoholic ferric chloride (Found: C, 45.5; H, 3.5.  $C_8H_7O_6N$  requires C, 45.1; H, 3.3%). The solution in alkali was crimson.

2-Nitro-3:4-dicarbethoxyphenylacetic acid. The phenolic acid (above) (1 mol.) was placed in a flask fitted with a mercury-sealed stirrer and swept out by a current of hydrogen. The flask was cooled in ice, and N sodium carbonate solution (5 mol.) was added. The deep red solution was then treated with chloroformic ester (1.1 mol.) which was run in from a burette, and the colour rapidly changed to pale yellow. Charcoal was added to remove a small amount of insoluble oil, and the filtered solution was acidified with ice-cold hydrochloric acid. The resulting oil was taken up in ether, the ether extracted with aqueous potassium bicarbonate, and the product obtained from this by acidification and extraction with benzene. When the benzene solution was evaporated to small volume, the dicarbethoxyphenylacetic <sup>acid</sup> crystallised in colourless needles, m.p.  $115^{\circ}$  after softening at  $105^{\circ}$  (Found: C, 47.4; H, 4.3.  $C_{14}H_{15}O_{10}N$  requires C, 47.1; H, 4.2%). This acid formed colourless solutions in cold dilute sodium carbonate and bicarbonate, but hydrolysis took place on standing, and was instantaneous in sodium hydroxide. The results obtained by benzylating 2-nitro-3:4-dihydroxyphenylacetic acid were similar

to those described in the case of 2-nitro-3-methoxy-4-hydroxyphenylacetic acid.

5:6-Dimethoxyanthranilcarboxylic acid. A solution of 2-nitro-3:4-dimethoxyphenylacetic acid in N sodium hydroxide was boiled under reflux for 50 hours, and acidified. The resulting yellow precipitate was crystallised first from water and then from benzene, and the product formed orange needles, m.p.  $175^{\circ}$  (decomp.), which yielded a colourless solution in sodium hydroxide (Found: C, 54.1; H, 4.2; N, 6.3.  $C_{10}H_9O_5N$  requires C, 53.8; H, 4.0; N, 6.3%).

6-Nitro-3:4-Dimethoxyphenylacetic acid. This acid was prepared both by the condensation of 6-nitrohomoveratrole with oxalic ester (Oxford and Raper, J.1927, 417) and by the nitration of 3:4-dimethoxyphenylacetic acid which was obtained from veratraldehyde by Mauthner's method (loc.cit.). A mixture of 3:4-dimethoxyphenylacetic acid (36g) and glacial acetic acid (80cc.) was stirred mechanically and cooled in ice. Fuming nitric acid (24cc.) in acetic acid (20cc.) was added slowly, and the mixture was poured into water. The precipitated acid was dried, and crystallised from glacial acetic acid in faintly yellow needles, m.p.  $206-207^{\circ}$ , or from ethyl acetate in colourless needles having the same melting point (Found: C, 50.0; H, 4.8.  $C_{10}H_{11}O_6N$  requires C, 49.8; H, 4.6%).

It was very sparingly soluble in benzene, chloroform, and cold water, and sparingly soluble in glacial acetic acid and ethyl acetate. Oxford and Raper record the melting-point as  $202-204^{\circ}$ , and state that the acid is "readily soluble in glacial acetic acid and in ethyl acetate". A specimen prepared by their method was identical in every respect with that just described.



PUBLICATION 17

ATTEMPTED SYNTHESSES OF PHENOLIC APORPHINES

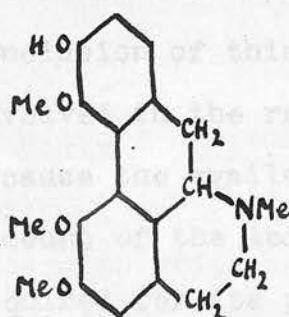
CORYDINE.

The work described in this paper was carried out personally by the author.

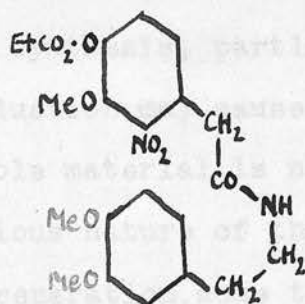
It was to be anticipated that the syntheses of the phenolic alkaloids of the aporphine series by the Bischler-Napieralski method would be a more difficult problem than that presented by the preparation of their ethers, and this has indeed proved to be the case. In the first place, it is essential to protect the hydroxyl groups during the early stages, such as the preparation of the acid chloride and the closure of the isoquinoline ring; but the protecting group, though stable, must be capable of being removed by comparatively mild reagents. Secondly, the protective group must not be removed in the process of working-up the nitrobenzylisoquinoline because the product, being then a nitrophenolic amine, would resemble in its properties the amino-acids, which are notoriously difficult to isolate. And finally, acid or alkaline solutions of the phenolic aporphines are sensitive to atmospheric oxidation, and this instability is to be expected in an even higher degree in the case of the phenolic aminobenzyltetrahydroisoquinolines.

It was decided to attempt in the first instance the synthesis of corydine (I). In the preceding paper, it was stated that the carbethoxy-group seemed to be suitable in many ways for use as a protective radical, and accordingly a chloroform solution of 2'-nitro-3'-methoxy-4'-carbethoxy-phenylaceto- $\beta$ -3:4:-dimethoxyphenylethylamide (II) was treated with phosphorus pentachloride. The Bischler-Napieralski

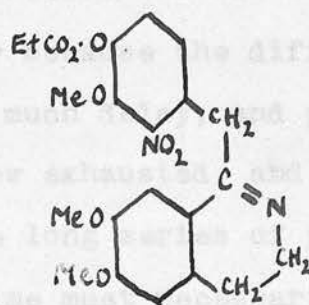
reaction did not proceed quite so smoothly as in the case of the fully methylated amides, since a certain amount of tarry material was produced, but 2'-nitro-3'-methoxy-4'-carbethoxybenzyl-6:7-dimethoxy-3:4-dihydroisoquinoline (III) was obtained by careful neutralisation of an ice-cold hydrochloric extract of the products of the reaction.



I



II

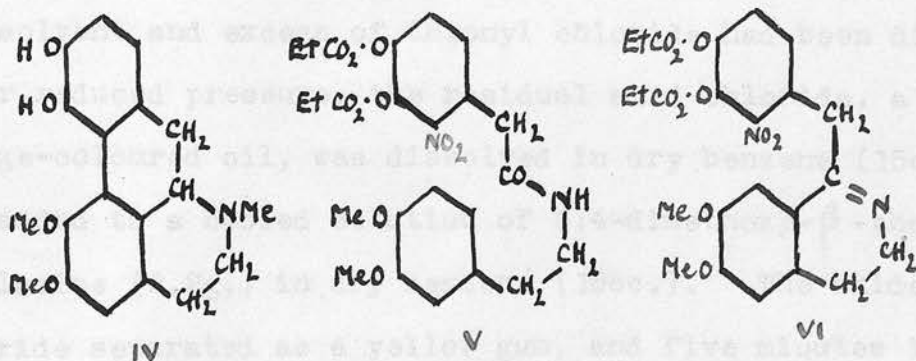


III

The methiodide of this base (III) was readily prepared by heating with methyl iodide, but the accomplishment of the next stage in the synthesis - reduction - has so far proved an unexpected stumbling-block. The reduction has been carried out under a large number of varied conditions by different reagents, and in each case the result has been the same, namely the formation of an uncrystallisable, phenolic, basic oil, from which no crystalline derivatives have been obtained. This base, which did not contain an indole nucleus, did not diazotise when treated with nitrous acid, nor did it yield a nitroso-compound which gave

Liebermann's reaction. The nature of this substance, therefore, is at present a matter of complete uncertainty, but it is hoped that further investigation may bring to light the correct conditions for the preparation of the desired aminobenzyltetrahydroisoquinoline.

The author has not put off the submission of this thesis in the hope of being able to record the satisfactory conclusion of this synthesis, partly because the difficulties involved in the reduction may cause much delay, and partly because the available material is now exhausted, and on account of the tedious nature of the long series of processes required for its preparation, some time must necessarily elapse before more is assessable.



Similar results have been obtained in a parallel research designed for the synthesis of corytuberine (IV). The amorphous 2'-nitro-3':4'-dicarbethoxyphenylaceto- $\beta$ -3:4-dimethoxyphenylethylamide (V) yielded crystalline 2'-nitro-

3':4'-dicarbethoxybenzyl-6:7-dimethoxy-3:4-dihydroisoquinoline (VI), from which the methiodide was readily obtained. The reduction of this compound with zinc and hydrochloric acid produced an uncrystallisable base which had properties analogous to those described in the preceding instance.

#### EXPERIMENTAL

2'-Nitro-3'-methoxy-4'-carbethoxybenzyl-6:7-dimethoxy-3:4-dihydroisoquinoline. 2-Nitro-3-methoxy-4-carbethoxyphenyl-acetyl chloride was prepared by heating on the water bath under reflux for 30 minutes a solution of the acid (2.8g.) and thionyl chloride (2.2cc.) in chloroform (15cc.). After the solvent and excess of thionyl chloride had been distilled under reduced pressure, the residual acid chloride, a pale orange-coloured oil, was dissolved in dry benzene (15cc.) and added to a cooled solution of 3:4-dimethoxy- $\beta$ -phenyl-ethylamine (2.2g.) in dry benzene (15cc.). The amide hydrochloride separated as a yellow gum, and five minutes later, dilute sodium carbonate solution was added. The benzene layer was separated, and the aqueous layer was extracted once with benzene; the mixed benzene solutions were washed with dilute hydrochloric acid and then with water, and dried with sodium sulphate. After the benzene had been evaporated,



2'-nitro-3'-methoxy-4'-carbethoxyphenylaceto- $\beta$ -3:4-dimethoxyphenylethylamide remained as an oil which could not be crystallised.

The amide (3.9g.) was dissolved in chloroform (35cc.) and treated with powdered phosphorus pentachloride (5g.). The mixture, protected from moisture, was then allowed to remain at room temperature for 48 hours, by which time a considerable quantity of crystalline material had separated from the brown solution. The solvent and phosphorus oxychloride were removed by distillation on the water bath under reduced pressure, and the yellow residue was dissolved in very dilute hydrochloric acid by heating on the water bath. This solution was cooled in ice, treated with animal charcoal, filtered, and rendered just alkaline with sodium carbonate, any rise in temperature being carefully avoided. 2'-Nitro-3'-methoxy-4'-carbethoxybenzyl-6:7-dimethoxy-3:4-dihydro-isoquinoline separated as a colourless precipitate, which was collected at the pump, washed with water, and crystallised twice from methyl alcohol. It formed faintly brown, sharp-ended prisms, m.p. 137° (Found: C, 59.7; H, 5.6.  $C_{22}H_{24}O_8N_2$  requires C, 59.5; H, 5.4%). Hydrolysis of the carbethoxy-group took place rapidly when the base was shaken with dilute sodium hydroxide (2N), but slowly in presence of cold dilute ammonia or when warmed with dilute sodium carbonate solution.

The methiodide was obtained by boiling a solution of the base (1.8g.) in methyl iodide (10cc.) on the water bath. Crystals soon filled the clear solution, and after the excess of methyl iodide had been distilled, the methiodide crystallised from methyl alcohol, from which it separated in stellar clusters of yellow needles, m.p. 160° (decomp.) (Found: C, 47.0; H, 4.8.  $C_{22}H_{24}O_8N_2MeI$  requires C, 47.1; H, 4.6%.

Reduction of the methiodide. Many reductions were carried out with zinc dust and hydrochloric acid, and wide variations were made in the following conditions: the concentration of acid; the temperature; the rate of addition of zinc dust; the concentration of the methiodide in the reducing solution. Several experiments were performed using stannous chloride, or tin, and hydrochloric acid, and other reagents employed were hydrogen and colloidal palladium, and sodium hydrosulphite. The results obtained are summarised in the theoretical section of this paper, and no useful purpose will be served by recording here the details of these experiments.

PUBLICATION 18  
-----

THE CONSTITUTION OF LAUROTETANINE. SYNTHESSES OF

2:3:6:7:-TETRAMETHOXYAPORPHINE

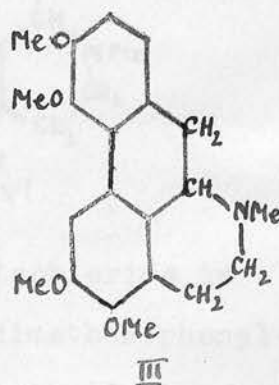
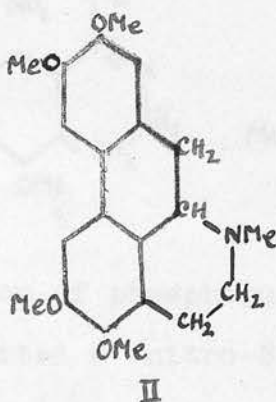
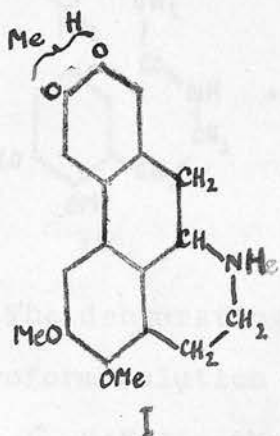
AND

3:4:6:7 -TETRAMETHOXYAPORPHINE.  
-----

Part of the work described in this paper was done personally by the author. The remainder of the experiments were carried out by Mr. R. K. Callow with the daily help and guidance of the author, and under his direction and supervision.

A résumé has been given in the theoretical section of this thesis of the arguments by which Gorter (Bull. jard. bot. Buitenzorg, 1921, iii, 3, 180) assigned the constitution (I) to laurotetanine, and aporphine alkaloid which occurs in the bark of the Javanese *Litsea citrata*. Gorter observed that the dimethyl-derivative of this alkaloid, isoglaucine, showed many similarities with glaucine, but did not appear to be identical with this base or with corytuberine dimethylether, and he therefore assigned to it the formula (II). The very recent work of Barger and Silberschmidt (J. 1928, November) and of Späth and Strauhal (Ber. 1928, November) has shown that isoglaucine is in reality impure glaucine, and does not therefore contain the vicinal homocatechol grouping in Ring III. Theoretical considerations, quite apart from the results of these investigators, convinced the author some time ago that this vicinal grouping does not occur in the aporphine series, and it then became evident that syntheses of 2:3:6:7:-tetramethoxyaporphine (II) and of 3:4:6:7:-tetramethoxyaporphine (III) would be of the greatest value in the elucidation of the true nature of laurotetanine. The inclusion of the base (III) as a possible structure for isoglaucine was the result of a careful comparison by the author of the colour reactions of all the aporphines, which

showed that the colours developed by the base (II) need not necessarily be those exhibited by glaucine (compare Gorter). 3:4:6:7:-Tetramethoxyaporphine and 2:3:6:7:-tetramethoxyaporphine were therefore prepared synthetically, and neither substance resembled Gorter's isoglaucine.\*

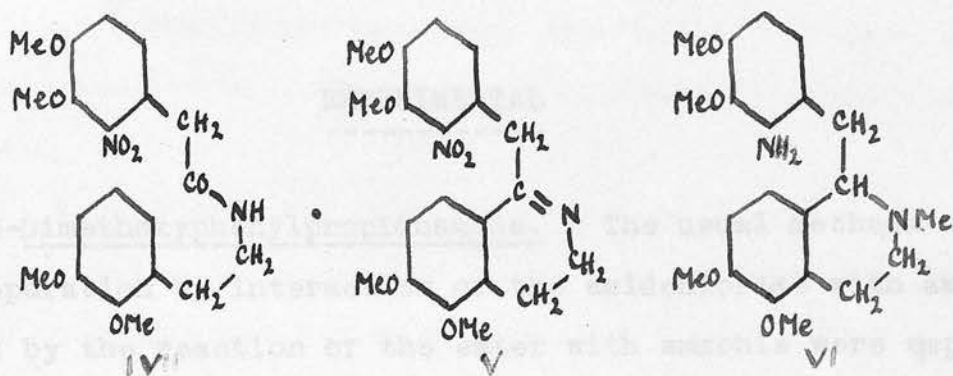


2'-Nitro-3':4'-dimethoxyphenylaceto- $\beta$ -2:3-dimethoxyphenylethylamide (IV), prepared by the interaction of 2-nitro-3:4-dimethoxyphenylacetyl chloride with 2:3-dimethoxy- $\beta$ -phenylethylamine, yielded 2'-nitro-3':4':5:6:-tetramethoxy-1-benzyl-3:4-dihydroisoquinoline (V) when submitted to the action of phosphorus pentachloride in chloroform solution. The reduction of the methiodide of the base (V) by zinc dust and hydrochloric acid produced 2'-amino-3':4':6:7-tetramethoxy-1-benzyl-2-methyl tetrahydroisoquinoline (VI), which was converted into dl-3:4:6:7-tetramethoxyaporphine by diazotisation in methyl alcoholic sulphuric acid. Resolution of this dl-base by means of d- and l-tartaric acids yielded d-3:4:6:7-

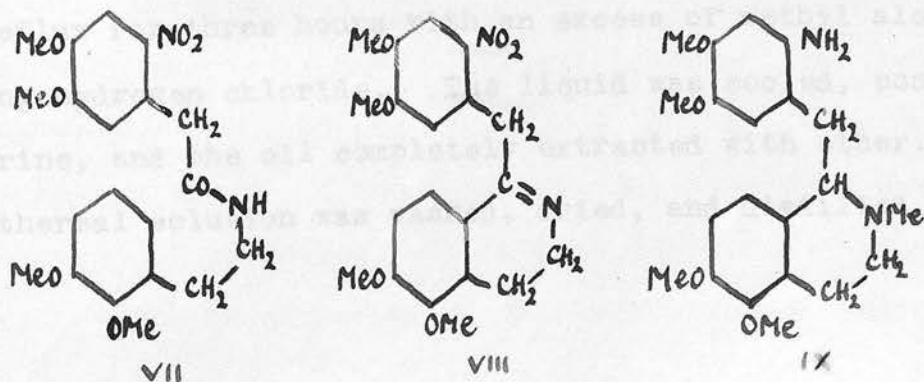
\*This result is of course to be expected in view of the more recent investigations.



tetramethoxyaporphine, m.p. 125-125.5°,  $[\alpha]_D^{20}$  168°, and 1-3:4:6:7-tetramethoxyaporphine, m.p. 125.5-126°,  $[\alpha]_D^{20}$  -167°. Details of these experiments are given in the experimental section.



The dehydrating action of phosphorus pentachloride in chloroform solution converted 6'-nitro-3':4'-dimethoxyphenyl-aceto-β-2:3-dimethoxyphenylethylamide (VII) into 6'-nitro-3':4':5:6-tetramethoxy-1-benzyl-3:4-dihydroisoquinoline (VIII) in a manner similar to that described in the preceding case. The methiodide of this base was reduced to 6'-amino-3':4':5:6-tetramethoxy-1-benzyl-2-methyltetrahydroisoquinoline (IX), which yielded dl-2:3:6:7-tetramethoxyaporphine when diazotised in methyl alcoholic sulphuric acid. Attempts to resolve this base by means of d- and l-tartaric acids were unsuccessful.



A number of other points of interest arose during the course of this work, and these are described in the experimental section.

#### EXPERIMENTAL

2:3-Dimethoxyphenylpropionamide. The usual methods of preparation by interaction of the acidchloride with ammonia and by the reaction of the ester with ammonia were employed.

(i) 2:3-Dimethoxyphenylpropionic acid (51.2 g.) (Perkin & Robinson, J.C.S., 1914, 105, 2387) was dissolved in chloroform (200 c.c.), thionyl chloride (50 c.c.) added, and the mixture allowed to remain at room-temperature for 40 hours. After removing some of the solvent under reduced pressure, the mixture was poured into concentrated ammonia solution (1 li.). Excess of ammonia and chloroform were removed by distillation. Most of the amide separated on cooling, and further quantities were obtained by evaporation of the mother-liquors. Yield, 48g., 95% of theory.

(ii) 2:3-Dimethoxyphenylpropionic acid (35g.) was heated under reflux for three hours with an excess of methyl alcohol containing hydrogen chloride. The liquid was cooled, poured into brine, and the oil completely extracted with ether. The ethereal solution was washed, dried, and distilled, finally

under reduced pressure. Methyl 2:3-dimethoxyphenylpropionate was collected at 166 - 176°/15mm. The ester (28 g.) and concentrated ammonia (250 c.c.) were shaken together for 40 hrs. A clear solution was obtained, from which, by evaporation of the excess of ammonia, crystals of the amide separated. Yield, 15.5 g.

Some difficulty was experienced in obtaining good analytical figures for the amide. A specimen prepared from the acid chloride was recrystallised from light petroleum (b.p. 80 - 100°), in which it was sparingly soluble, and separated as white needles. The colourless prisms of 2:3-dimethoxyphenylpropionamide, m.p. 97 - 99°, thus obtained were still impure. (Found: N, 7.2%.  $C_{11}H_{15}O_3N$  requires N, 6.7%). The impurity was not removed by a further recrystallisation. (Found: C, 64.2; H, 7.2; N, 7.3. Calc. C, 63.2; H, 7.2; N, 6.7%). A specimen of the amide prepared from the ester was distilled under reduced pressure and the fraction of b.p. 233 - 235°/16 mm. was collected and recrystallised from light petroleum. (Found: N, 6.5%; m.p. 97-98°.)

$\beta$ -2:3-Dimethoxyphenylethylamine. This was prepared from the amide in the usual way. The amide (50 g.) was treated with the sodium hypochlorite prepared from a solution of sodium hydroxide (50 g. in 500 c.c.) and chlorine from the calculated quantity of potassium permanganate (15 g.) and hydrochloric acid. The second stage of the reaction was completed by

adding potassium hydroxide (150 g.) and heating on the water bath. After being isolated by extraction with ether, the product was distilled, and  $\beta$ -2:3-dimethoxyphenylethylamine was collected at 145 - 155°/15 mm. (27 g.). On distillation with a short column, the bulk of the liquid boiled at 158 - 159°/25 mm.

2'-Nitro-3':4'-dimethoxyphenylaceto- $\beta$ -2:3-dimethoxyphenyl-ethylamide. A solution of 2-nitro-3:4-dimethoxyphenylacetyl chloride (from 19 g. acid) in dry benzene (70 cc.) was added slowly, to a cooled solution of  $\beta$ -2:3-dimethoxyphenylethylamine (14 g.) in dry benzene (30 cc.). A slight excess of 2N sodium hydroxide was added to the clear solution, and the benzene layer was separated. The aqueous layer was again extracted with benzene, and the combined extracts were washed with dilute acid and with water and evaporated. The tarry residue was with some difficulty induced to crystallise by rubbing with methyl alcohol (Yield, 26 g., m.p. 81 - 89°). After recrystallisation from a small quantity of methyl alcohol and from 60% ethyl alcohol, 2'-nitro-3':4'-dimethoxyphenylaceto- $\beta$ -2:3-dimethoxyphenylethylamide was obtained as colourless needles, m.p. 95 - 96°. (Found: N, 6.7.  $C_{20}H_{24}O_7N_2$  requires N, 6.9%). The amide was very soluble in benzene, readily soluble in methyl or ethyl alcohol, fairly soluble in carbon tetrachloride, and insoluble in light petroleum.



2'-Nitro-5:6:3':4'-tetramethoxy-1-benzyl-3:4-dihydroisoquinoline. The amide (4.5 g.) was mixed with phosphorus pentachloride (5 g.) in chloroform suspension (30 c.c.) and kept in a closed vessel. After 36 hrs. a mass of nodular crystals had separated. These appeared to consist of an additive compound of the product with phosphorus pentachloride or phosphoryl chloride, since a portion of the solid, when separated and washed with chloroform, was highly hygroscopic, and the solution in water gave strong positive reactions for both phosphate and chloride. The reaction-mixture was poured into water, the chloroform boiled off, and the solution filtered from the residual tar. Addition of excess of ammonia yielded a gummy precipitate which soon solidified (Yield, 2.5 g.). When recrystallised twice from methyl alcohol, 2'-nitro-5:6:3':4'-tetramethoxy-1-benzyl-3:4-dihydroisoquinoline was obtained as peach-coloured prisms, m.p. 152 - 156° to a red liquid. (Found: C, 62.4; H, 5.7.  $C_{20}H_{22}O_6N_2$  requires C, 62.2; H, 5.7%).

The methiodide was prepared by dissolving the base in excess of boiling methyl iodide and allowing the solution to cool. The product separated in clusters of small needles containing methyl iodide of crystallisation, m.p. 110 - 116° (effervescence). Found: Loss at 95°: 20.3.  $C_{21}H_{25}O_6N_2I$ ,  $CH_3I$  requires 21.2%). After drying at 95° the methiodide melted at 183 - 184° (decomp.) (Found: C, 47.8;



H, 5.1.  $C_{21}H_{25}O_6N_2I$  requires C, 47.7; H, 4.7%). The methiodide could not be recrystallised satisfactorily, and the specimen used for analysis was prepared from the pure base. The methiodide was very soluble in methyl or ethyl alcohol, and in chloroform, very sparingly soluble in carbon tetrachloride.

2'-Amino-5:6:3':4'-tetramethoxy-1-benzyl-2-methyltetrahydro-  
isoquinoline.

The methiodide (6 g.) was suspended in a mixture of hydrochloric acid (120 cc.) and water (80 cc.), heated on the water bath, and zinc dust (18 g.) added gradually until the solution was completely decolourised. The solution was filtered while hot, and basified with concentrated ammonia solution. The purple solution was extracted with ether (500 cc.), the extract dried over sodium sulphate and evaporated to dryness. A mixture of crystals with a little gum separated (Yield, 3.7 g.). An attempt to isolate the product by passing hydrogen chloride into the ethereal solution yielded a sticky product which could not be obtained crystalline, and the above method was more satisfactory. When purified by recrystallisation from ether, 2'-amino-5:6:3':4'-tetramethoxy-1-benzyl-2-methyltetrahydroisoquinoline was obtained as colourless rhombic plates, m.p. 117.5 - 119.5° (Found: C, 67.7; H, 7.4.  $C_{21}H_{28}O_4N_2$  requires C, 67.7; H, 7.5%).

Diazotisation of the amine in hydrochloric acid, and addition of the solution to an alkaline solution of  $\beta$ -naphthol, yielded a scarlet precipitate of an azo-dye.

dl-3:4:6:7-Tetramethoxyaporphine.

The preceding amine (3.72 g.) was dissolved in a mixture of 2N sulphuric acid (20 cc.) and methyl alcohol (20 cc.). The solution was cooled in a freezing-mixture and diazotised by slowly adding the calculated amount of standardised sodium nitrite solution (5.1 cc.) containing 0.1378 g. / cc.). After allowing the mixture to remain for twenty minutes, it was boiled on the water-bath for  $\frac{1}{2}$  hour. Concentrated hydrochloric acid (6.cc.) was then added, and zinc dust (2 g.) added slowly. When the zinc dust had dissolved, the solution was cooled, and made strongly alkaline by the addition of sodium hydroxide. The solution was then extracted with ether (900 cc.). The product was only slowly extracted, and this large volume of ether was found to be necessary. The ethereal solution was dried over sodium sulphate and evaporated. The gummy residue was dissolved in the minimum quantity of hydrochloric acid (1:1) and excess of sodium iodide added. A gum separated; the supernatant liquid was poured off, and the gum stirred with methyl alcohol (20 cc.). dl-3:4:6:7-Tetramethoxyaporphine hydriodide was thus obtained as a white powder.

It formed long prisms from methyl alcohol, m.p. 257 - 262° after darkening. (Found: C, 52.6; H, 5.4.  $C_{21}H_{25}O_4N$ , HI requires: C, 52.2; H, 5.4%). The free base was obtained by grinding the hydriodide with a slight excess of sodium hydroxide; the solid was collected by filtration and dried. (Yield, 0.87 g., m.p. 122 - 127°). When purified by repeated recrystallisation from light petroleum, dl-3:4:6:7-tetramethoxyaporphine was obtained as clear yellow plates, m.p. 131 - 132°. (Found, by microanalysis: C, 70.9; H, 7.2.  $C_{21}H_{25}O_4N$  requires C, 71.0; H, 7.0%). The substance was very soluble in methyl and ethyl alcohols, acetone, benzene, and ether, but insoluble in water.

#### Resolution of dl-3:4:6:7-Tetramethoxyaporphine.

The crude base (0.7404 g.) was treated with a saturated solution of d-tartaric acid (1 mol., 0.3336 g.) in absolute alcohol. No separation took place after keeping for some time, but a caseous precipitate (0.5 g.) was obtained finally by the addition of benzene to a solution in slightly aqueous alcohol. The filtrate yielded a gum (0.7 g.) on evaporation to dryness. The precipitate after being twice recrystallised from 96% alcohol, yielded d-3:4:6:7-tetramethoxyaporphine d-bitartrate in bunches of needles, m.p. 174 - 185° after

softening. (Found: Loss at 80° in a vacuum over  $P_2O_5$ : 6.4; 7.0. Loss at 110° in a vacuum over  $P_2O_5$ , 7.3. Calc. for loss of  $2H_2O$  from  $C_{25}H_{31}O_{10}N$ ,  $2H_2O$ : 6.7%). The anhydrous salt regained water rapidly in the air. When heated at 110° slight decomposition occurred, for the salt then crystallised poorly from alcohol, and low values were obtained for the rotation of the salt and of the base as compared with the optical isomerides. Concordant values were obtained, however, with a specimen obtained by repeating the process of resolution. In water, the d-bitartrate had  $[\alpha]_D^{21} = 84.9^\circ$  ( $c = 0.930$ ). The base was liberated from the bitartrate by sodium hydroxide and extracted with chloroform. The residue left by evaporation of the chloroform was recrystallised from light petroleum, yielding d-3:4:6:7-tetramethoxyaporphine as long, pale-yellow prisms, m.p. 125 - 125.5°. In chloroform, ( $c = 0.459$ ),  $[\alpha]_D^{20} = 168^\circ$ .

From mother-liquors and residues of the isolation of the d-base d-bitartrate, the base was set free, extracted with ether, and the extracts evaporated in a weighed dish. The gum (0.4955 g.) thus obtained was treated with l-tartaric acid (0.2235 g.) in alcohol. Crystals readily separated from the solution, and after three recrystallisations from alcohol, l-3:4:6:7-tetramethoxyaporphine l-bitartrate was obtained as needles, m.p. 170 - 180° after softening.

(Found: by microanalysis: Loss at  $100^{\circ}$  over  $P_2O_5$  in a vacuum; 7.5%; and, in anhydrous material, C, 58.7; H, 6.1. Calc. for  $C_{25}H_{31}O_{10}N$ ,  $2H_2O$ : Loss 6.7%.  $C_{25}H_{31}O_{10}N$  requires C, 58.1; H, 6.1%). In water ( $c = 2.044$ ),  $[\alpha]_D^{18.5} = -85.2^{\circ}$ . l-3:4:6:7-Tetramethoxyaporphine was obtained from this salt, and formed long, pale-yellow prisms from light petroleum, m.p.  $125-5 - 126^{\circ}$ . In chloroform ( $c = 0.978$ ),  $[\alpha]_D^{20} = -167^{\circ}$  (Found, by microanalysis: C, 70.8; H, 6.8.  $C_{21}H_{25}O_4N$  requires C, 71.0; H, 7.0%).

l-3:4:6:7-Tetramethoxyaporphine methiodide was prepared by warming the *l*-base with excess of methyl iodide. A white solid separated and melted at  $208 - 210^{\circ}$ , after <sup>being</sup> freed from methyl iodide by heating on the water bath.

The following colour-reactions were given by the *l*-base: Concentrated sulphuric acid: Very pale green, or blue-green in larger amount. Changed to orange-red by addition of nitric acid.

Concentrated nitric acid: Immediate orange-red colour.

Fröhde's Reagent: Barely perceptible straw colour.

Erdmann's Reagent: Immediate deep greenish-blue, changing quickly to orange-red.

Mandelin's Reagent: Deep blue-green, changing to brown.



6-Nitro-3:4-dimethoxyphenylacetic acid. This was prepared by nitration of 3:4-dimethoxyphenylacetic acid, and also from 6-nitrohomoveratrole (by way of 6-nitro-3:4-dimethoxyphenylpyruvic acid) by the method described by Oxford and Raper (J.C.S., 1927. 417). In the latter case, the yield of 6-nitro-3:4-dimethoxyphenylpyruvic acid was improved by increasing the proportions of potassium ethoxide and ethyl oxalate to 6-nitrohomoveratrole. The quantities used by Oxford and Raper for 50 g. of 6-nitrohomoveratrole were used for 41 g., with an increase in the yield from 60% to 77% of the theoretical. Potassium (9.9 g.) was pulverised by vigorous mechanical stirring under boiling benzene (250 cc.). After the liquid had been allowed to cool, and ether (250 cc., dry and free from alcohol) had been added, a solution of absolute alcohol (14.5 cc.) in dry ether (15 cc.) was slowly run in to the stirred mixture. After  $\frac{1}{2}$  hour, ethyl oxalate (37.2 g.) was added, followed by a solution of 6-nitrohomoveratrole (41 g.) in dry benzene (300 cc.). The mixture, protected from atmospheric moisture and carbon dioxide, was kept at 35 - 40° for 24 hours and stirred continuously. Water (500 cc.) was now added, and the purple aqueous layer, after separation, was washed with a little benzene and acidified with a slight excess of dilute hydrochloric acid.

6-Nitro-3:4-dimethoxyphenylpyruvic acid separated as a copious sandy precipitate (42 g.).

The process for conversion of the pyruvic acid into the acetic acid was also modified. The 6-nitro-3:4-dimethoxyphenylpyruvic acid (42 g.) was dissolved in 2N sodium hydroxide (300 cc.). The solution was cooled in ice, and "perhydrol" was added slowly until the violet colour disappeared. A small quantity of white, slimy precipitate was removed, and the filtrate acidified with dilute sulphuric acid. The precipitated 6-nitro-3:4-dimethoxyphenylacetic acid was collected and dried. Yield, 31 g. (83% of theory), m.p. 203-204° (decomp). Recrystallised from alcohol, the acid was obtained as brown needles, m.p. 204 - 205° (206 - 207°, corr.) Oxford and Raper (loc.cit.) give 203 - 204°.

6'-Nitro-3':4'-dimethoxyphenylaceto- $\beta$ -2:3-dimethoxyphenylethylamide.

Preliminary experiments showed that 6-nitro-3:4-dimethoxyphenylacetyl chloride could not be prepared in the same way as the 2-nitro-derivative. When the mixture of the acid with thionyl chloride in benzene was gently warmed, decomposition occurred with blackening, and no crystalline amide could be prepared from the product obtained after removal of thionyl chloride. Further, when the acid was heated with  $\beta$ -2:3-dimethoxyphenylethylamine at 135°, carbon dioxide was lost,

with the formation of 6-nitrohomoveratrole. The chloride appeared to be formed smoothly when slightly more than one molecular proportion of phosphorus pentachloride was added to a suspension of the acid in chloroform. Heating or the addition of pyridine to this solution caused decomposition. The liquid darkened considerably, and no amide could be separated from the tarry product obtained after addition of  $\beta$ -2:3-dimethoxyphenylethylamine and treatment in the usual way. Some of the desired product was obtained however by the addition of an excess of the amine to the solution containing the acid chloride, and finally the following process was adopted. The acid (13.1 g.) was suspended in dry chloroform, and phosphorus pentachloride (25 g.) added slowly. After shaking for 20 minutes, all the phosphorus pentachloride and acid had passed into solution. This solution was then added slowly to a vigorously stirred mixture of the amine (12 g.) in chloroform (50 cc.) and dilute sodium hydroxide (250 cc. of 2N solution and 400 cc. of water) cooled in ice. After about 20 minutes the chloroform was separated, the aqueous layer extracted with chloroform, and the combined chloroform solutions washed with dilute acid, dried, and evaporated. The residual gum was boiled with methyl alcohol. On cooling the product separated in white needles (9.5 g.). Recrystallised from methyl

alcohol and from benzene, pure 6'-nitro-3':4'-dimethoxyphenylaceto- $\beta$ -2:3-dimethoxyphenylethylamide separated as white needles containing no solvent of crystallisation, m.p. 144.5 - 145.5°. (Found: C, 59.8; H, 6.2.  $C_{20}H_{24}O_7N_2$  requires C, 59.4; H, 5.9%).

6'-Nitro-5:6:3':4'-tetramethoxy-1-benzyl-3:4-dihydroisoquinoline. The amide (9.5 g.) was added to a solution of phosphorus pentachloride (11 g.) in chloroform (60 cc.), and the mixture was kept in a closed vessel. Separation of nodular crystals began after three days, and appeared to be complete after four days. The mixture was poured into dilute hydrochloric acid, the chloroform boiled off, and the residual tar removed by filtration. When the filtrate was made alkaline with ammonia, a tar was precipitated which soon solidified (6 g.). When purified by crystallisation from methyl alcohol, in which it was sparingly soluble, and from benzene, in which it dissolved rather readily, 6'-nitro-5:6:3':4'-tetramethoxy-1-benzyl-3:4-dihydroisoquinoline was obtained as colourless prisms, m.p. 187.5 - 189.5° (Found: C, 62.2; H, 5.9.  $C_{20}H_{22}O_6N_2$  requires C, 62.2; H, 5.7%). This substance melted to a deep-red liquid, the colour fading on resolidification. The cyclisation was incomplete, for the tar which was insoluble in hydrochloric



acid yielded 1.0 g. of unchanged amide on treatment with alcohol.

The methiodide was prepared by heating the base (3.1 g.) with purified methyl iodide under reflux for 12 hours. The methiodide separated as yellow crystals, m.p.  $111^{\circ}$  (decomp. with effervescence) (4.95 g.). Good analytical figures could not be obtained for this substance. When it was recrystallised from absolute alcohol, it tended to separate as an oil, which solidified only on scratching the side of the vessel. This solid, m.p.  $146 - 147^{\circ}$  (with decomposition to a red liquid after softening at  $140^{\circ}$ ) was collected and dried in a vacuum. (Found: C, 50.2; H, 5.3.  $C_{21}H_{25}O_6N_2I$  requires C, 47.7; H, 4.7%). The solution in alcohol was red, and when crystallisation took place slowly in a not too concentrated solution, a mixture of yellow and red crystals separated, m.p.  $115 - 124^{\circ}$  (decomp.). An apparently homogeneous product was slowly precipitated as a yellow powder, m.p.  $146 - 148^{\circ}$  (decomp., softening at  $140^{\circ}$ ) when an excess of benzene was added to a solution of the methiodide in absolute alcohol. (Found: C, 49.6; H, 5.4.  $C_{21}H_{25}O_6N_2I$  requires C, 47.7; H, 4.7%). The analytical figures do not correspond to any simple addition of solvent. When heated at  $100^{\circ}$  the substance darkened slowly and the m.p. fell to  $108 - 120^{\circ}$  (decomp. at  $137^{\circ}$ ).



When the methiodide was ground with concentrated ammonia solution, a dark-red substance was formed which was extracted by benzene as a deep-red solution. An attempt to separate the product, presumably a 1-benzylidene-2-methyltetrahydroisoquinoline compound (cf. Gulland and Haworth, J.C.S., 1927, 2085), by the crystallisation from light petroleum of the tarry residue left by evaporation of the benzene solution, yielded black crystalline nodules, melting indefinitely at 55 - 60°, and red and yellow flocculent fractions, melting indefinitely at 60 - 70°. The material became yellow on treatment with dilute hydrochloric acid, dissolving to a yellow solution from which sodium iodide precipitated the methiodide. The methosulphate of the base, prepared on a small scale by heating the base with methyl sulphate in benzene, behaved similarly with ammonia solution.

6'-Amino-5:6:3':4'-tetramethoxy-1-benzyl-2-methyltetrahydroisoquinoline. The methiodide (3.5 g.) was suspended in a mixture of concentrated hydrochloric acid (80 cc.) and water (35 cc.), the mixture heated on the water bath, and zinc dust (25 g.) added slowly until the solution was decolourised. The solution was filtered, basified

with an excess of ammonia, and the mixture extracted thoroughly with ether. Evaporation of the ethereal solution yielded a gum which could not be induced to crystallise. The gum was dissolved in chloroform and dry hydrogen chloride passed. On addition of ether, a copious white precipitate was formed which was collected. (2.2 g.). When purified by two recrystallisations from absolute alcohol, 6'-amino-5:6:3':4'-tetramethoxy-1-benzyl-2-methyltetrahydroisoquinoline dihydrochloride was obtained as microscopic short needles, m.p. 233.5 - 235° (decomp.). (Found: C, 56.7; H, 6.8.  $C_{21}H_{28}O_4N_2 \cdot 2HCl$  requires C, 56.6; H, 6.8%). The addition of sodium nitrite to the solution in dilute hydrochloric acid caused the development of a deep-blue colouration, which faded in a few minutes through blue-green to yellow. A red precipitate of an azo-dye was obtained when the solution was added to an alkaline solution of  $\beta$ -naphthol.

dl-2:3:6:7-Tetramethoxyaporphine.

The preceding dihydrochloride (1.94 g.) was dissolved in a mixture of methyl alcohol (10 cc.) and 2N sulphuric acid (10 cc.). The solution was cooled in a freezing-mixture and the calculated quantity of standardised sodium nitrite solution (2.2 cc., 0.1378 g./cc.) added slowly.

After <sup>remaining</sup> ~~keeping~~ at ordinary temperature for 2 hours, the solution was boiled under reflux for 1 hour. Concentrated hydrochloric acid (3 cc.) was then added, and the mixture reduced by the gradual addition of zinc dust (1 g.). The solution was then filtered, rendered alkaline with an excess of sodium hydroxide, and extracted thoroughly with ether. The ethereal extract, dried over sodium sulphate, yielded a gum on evaporation. This was dissolved in dilute hydrochloric acid and excess of sodium iodide added. The supernatant liquid was poured off from the precipitated gum, which yielded a white powder when stirred with alcohol. The crude hydriodide thus obtained (0.55 g.) was collected and dried. It darkened above 200° and melted at 227.5 - 230.5° with decomposition. When the hydriodide was ground with sodium hydroxide solution, a brown viscous oil was formed, which was extracted with chloroform, and the extract dried and evaporated. dl-2:3:6:7-tetramethoxy-aporphine, m.p. 115.5 - 116.5°, in the form of very pale yellow nodules, was obtained from the gummy residue by repeated recrystallisation from light petroleum (b.p. 60 - 80°). (Found, by microanalysis: C, 71.0; H, 6.9.  $C_{27}H_{25}O_4N$  requires C, 71.0; H, 7.0). The methiodide was prepared by warming the base with a little alcohol and excess of methyl iodide. The white solid which separated was freed

from solvent by heating on the water bath and recrystallised from a large volume of methyl alcohol, from which it separated as colourless needles, m.p. 204 - 208°.

An attempt was made to resolve the dl-base by forming the d-bitartrate, but this could only be obtained as a gum. By fractional separation from absolute alcohol and conversion of the more soluble fraction into the l-bitartrate, two gums were obtained which did not become crystalline on repeated separation from absolute alcohol. Both yielded the unchanged base, m.p. 115.5 - 116.5°, which showed no evidence of optical activity.

The following colour-reactions were given by the dl-base:

Concentrated Sulphuric Acid:	Emerald green, becoming intensely green on warming, and red on dilution.
Concentrated Nitric Acid:	Indigo, becoming deep purple and finally brown on warming.
Fröhde's Reagent:	Colourless
Erdmann's Reagent:	Deep reddish-purple.
Mandelin's Reagent:	Transient green, becoming reddish-purple and finally brown.



Colour Reactions of the Aporphines

Aporphine	Mandelin	Erdmann	Fröhde	H <sub>2</sub> SO <sub>4</sub>	HNO <sub>3</sub>
Glaucine	green, blue violet	blue, green- blue	green, blue indigo, violet	nil, deep blue at 100°	green deep red
Laurotetan- ine	indigo, brown, yellow	deep blue, brown, violet	indigo, brown	rose-red green-blue violet @ 100°	red- brown
Bulbocap- nine	blue, darker	blue, blue- violet	dark blue	orange, violet	red brown
Bulbocap- nine methylether	red, violet, blue	deep red	deep green-blue	nil, orange red	-
Corytuber- ine	grey-blue dark green	green, blue- violet	steel-blue indigo blue-green	nil, green red, violet	blood- red
Corytuber- ine dimethyl ether	pale red, green olive	nil, bright- green	nil, moss-green	nil	instant blood- red
Corydine	transient violet, green	emerald	malachite- green	nil	blood- red
Isocorydine	violet	pale yellow green	pale violet green-brown	nil	red- brown
Dicentrine	deep blue	nil, soon blue	deep blue, green-blue, violet	nil, soon violet- red	nil, blue- green, yellow, brown
Epidicentr- ine	-	-	-	red- violet	blue- green
Domesticine & Iso-D.	-	-	-	-	blue
5:6-Dimethoxy	green, soon brown	pink- purple	deep blue- purple	nil	-



Aporphine	Mandelin	Erdmann	Fröhde	H <sub>2</sub> SO <sub>4</sub>	HNO <sub>3</sub>
3:4:6:7-Tetramethoxy	deep blue-green soon brown	instant green-blue, orange-red	pale straw	pale green	orange-red
2:3:6:7-Tetramethoxy	instant green, red-purple, dull brown	deep red-purple	nil	emerald, intense green @ 100°, red with H <sub>2</sub> O	indigo, purple @ 100°, brown
Morphothebaine	dirty violet, lighter	yellow, reddish	steel-blue, grey-blue, tinge violet, yellow-green	nil	blood-red, red-brown
Morphothebaine dimethyl ether	violet, brown	pale yellow	dull green	nil	bright brown, duller
Isothebaine	olive, brown	yellow	blue, green olive, bright-green	nil	dark violet red-brown yellow
Isothebaine methylether	olive-green, dull brown	yellow	nil, bright green	nil	dark violet red-violet, brown
Apomorphine	instant green, indigo, dull green	dull green blood-red	violet, brown, dull purple	pale straw brown-violet @ 100°	purple-red, orange-red @ 100°
Boldine	-	green	-	blue (in HAcO.)	-
Glaucidine	-	green, blue brown-red	dull blue dull green, violet	instant red-violet, nil, green, green-blue	brown

PUBLICATION 19.

THE CONSTITUTION OF ISOTHEBAINE.

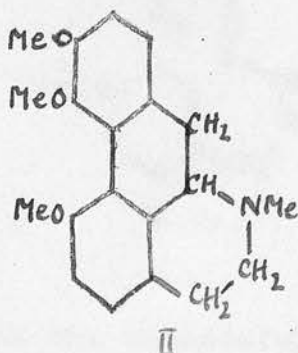
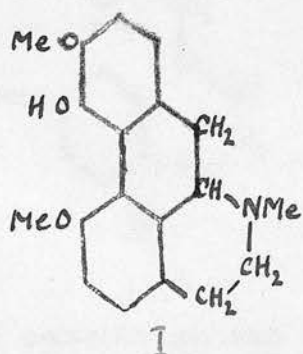
ATTEMPTED SYNTHESIS OF 3:4:5-TRIMETHOXYAPORPHINE.

The work described in this paper was done in collaboration with Mr. R.K. Callow, who performed the experiments under the author's supervision and with the daily help and guidance of the author.

In 1914, Klee (Arch. Pharm. 1914. 252, 211) assigned the constitution (I) to isothebaine, the phenolic alkaloid which occurs in *Papaver orientale* after the period of blooming and the withering of the aerial parts. There can be little doubt that Klee was correct in designating isothebaine an aporphine alkaloid; its general reactions show conclusively that it contains the ring-system of apomorphine and morphothebaine. On the other hand, the location of the oxygen atoms in positions 3,4, and 5 was based on more slender evidence. Thus, Klee converted isothebaine by exhaustive methylation, oxidation of the vinyl group, and elimination of carbon dioxide, into a trimethoxyphenanthrene picrate (m.p. 160°) which he considered was impure 3:4:5-trimethoxyphenanthrene picrate (m.p. 166°) (Pschorr, Ann. 1912. 391. 40). This conclusion, although possibly correct, clearly requires confirmation, more especially since the alternation of thebaine and isothebaine as the chief alkaloid of *Papaver orientale* renders the latter base one of the most interesting members of the aporphine series.

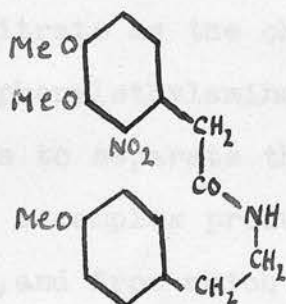
No later publication on the subject is recorded, possibly on account of the difficulty of obtaining a supply of isothebaine, and an attempt was therefore made to synthesise 3:4:5-trimethoxyaporphine (II) by the Bischler-Napieralski method in order to compare its properties with those of isothebaine methylether. It must be confessed,

however, that this work was initiated with some misgiving, since it seemed extremely doubtful if the activation of the nucleus of the requisite  $\beta$ -phenylethylamine would be sufficient to allow the formation of the isoquinoline ring to proceed in a normal manner.

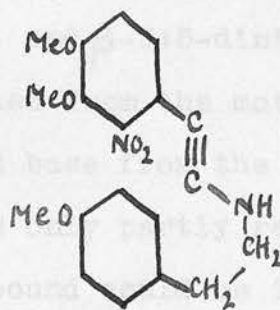


2'-Nitro-3':4'-dimethoxyphenylacetic- $\beta$ -4-methoxyphenylethylamide (III) was prepared from 2-nitro-3:4-dimethoxyphenylacetyl chloride and  $\beta$ -4-methoxyphenylethylamine (Barger and Walpole, J. 1909. 95. 1720), but this amide could not be induced to form a benzylisoquinoline under any of the conditions which were tried. No reaction took place with phosphorus pentachloride in a cold chloroform solution, whilst the action of phosphoric oxide on the amide in boiling toluene yielded 2'-nitro-3':4'-dimethoxyphenyl-( $\beta$ -4-methoxyphenylethylamino)acetylene (IV), isomeric with the isoquinoline derivative but devoid of basic properties. This substance was probably analogous to the non-basic compound

which Kay and Pictet (J. 1913. 103. 947) obtained from 2-nitro-3:4-dimethoxyphenylacetic- $\beta$ -phenylethylamide as the result of a similar reaction.



III



IV

The conclusion was drawn that the successful closure of the isoquinoline ring is dependent on the presence of a strongly para-directive group in the para-position to that at which condensation is to take place. It was hoped therefore that the introduction of such a para-directive group into the 5-position of the nucleus of  $\beta$ -4-methoxyphenylethylamine would enhance the reactivity at the 2-position sufficiently to allow ring-formation to be successfully carried out. The acylamino-group was the most suitable for this purpose, since it was essential that the group selected should be capable of being removed at a later stage. Experiments were therefore instituted in order to determine the most convenient method of introducing an amino-group into the 5-position of  $\beta$ -4-methoxyphenylethylamine by the

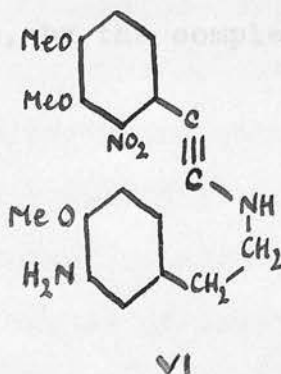
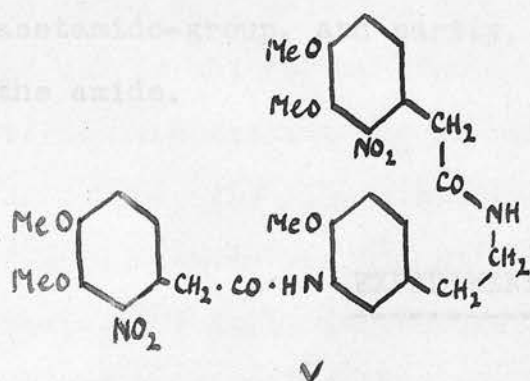


nitration and reduction of the amine itself or of one of the intermediate compounds in its preparation.

Nitration of  $\beta$ -4-methoxyphenylethylamine in fuming nitric acid yielded  $\beta$ -3:5-dinitro-4-methoxyphenylethylamine nitrate as the chief product, and  $\beta$ -3:5-dinitro-4-hydroxyphenylethylamine was separated from the mother-liquors. Attempts to separate the methylated base from the nitrate yielded a complex product, which was only partly redissolved by acid, and from which no pure compound could be isolated. Nitration took place only to a small extent in presence of excess of urea nitrate, and nitration of the hydrochloride in acetic was also unsuccessful. Nitration of the sulphate in concentrated sulphuric acid yielded only  $\beta$ -3-nitro-4-methoxyphenylethylamine-5-sulphonic acid. The attempt to nitrate at this stage was, therefore, abandoned.

The nitration of  $\beta$ -4-methoxyphenylpropionic acid, on the other hand, took place readily. The action of concentrated nitric acid yielded  $\beta$ -3-nitro-4-methoxyphenylpropionic acid, accompanied by small quantities of  $\beta$ -3:5-dinitro-4-hydroxyphenylpropionic acid. The occurrence of a demethylated, dinitrated, by-product in this case and in the nitration of  $\beta$ -4-methoxyphenylethylamine may be compared with the result obtained by Thoms and Drauzburg (Ber., 1911, 44. 2125) in the nitration of dihydroanethol, which yielded considerable

quantities of dinitropropylphenol. The mononitro-acid was converted into the amide, and the latter into  $\beta$ -3-nitro-4-methoxyphenylethylamine, which was reduced to  $\beta$ -3-amino-4-methoxyphenylethylamine. The action of 2-nitro-3:4-dimethoxyphenylacetyl chloride on this amine yielded 2'-nitro-3':4'-dimethoxyphenylaceto- $\beta$ -3(2"-nitro-3":4"-dimethoxyphenylacetamido)-4-methoxyphenylethylamide (V).



It was not found possible to acylate the aliphatic amino-group separately, and this double amide was, therefore, the only compound available for application of the isoquinoline synthesis. The action of phosphorus pentachloride on the amide in cold chloroform solution yielded a very weakly basic tarry product, which formed a picrate, but no pure substance could be isolated. Hydrolysis of the crude product by boiling concentrated hydrochloric acid yielded a base (VI), containing a primary amino-group, which was purified by way

of its picrate. This base was isomeric with the desired aminobenzylisoquinoline, but the benzoyl derivative was insoluble in acid, and this fact, combined with the feeble basicity of the 2-nitro-3:4-dimethoxyphenylacetyl derivative from which it was originally obtained by hydrolysis, indicated that the reaction had taken the same course as in the previous case. This behaviour may be largely accounted for by the insufficient activation by the 2-nitro-3:4-dimethoxyphenyl-acetamido-group, and partly, perhaps, by the complexity of the amide.

#### EXPERIMENTAL

$\beta$ -4-Methoxyphenylethylamine. This chain of reactions was used by Barger and Walpole (J.C.S., 1909, 95, 1720) in the first synthesis of  $\beta$ -4-methoxyphenylethylamine, but different methods have now been employed.

$\beta$ -Methoxycinnamic acid. Anisaldehyde (120 g) and malonic acid (200 g.) in pyridine (320 cc.) and piperidine (7 cc.) were heated on the water-bath for  $1\frac{1}{2}$  hours. The solution was boiled for ten minutes, cooled, and poured into excess of dilute hydrochloric acid, when the cinnamic acid was precipitated. Yield, 92% of theory.

$\beta$ -4-Methoxyphenylpropionic acid. The crude cinnamic acid was dissolved in 8-9 parts of water containing an equivalent amount of potassium carbonate and reduced by the gradual addition of 12 parts of 4% sodium amalgam at a temperature just below boiling-point. After filtration, the solution was acidified and the precipitated phenylpropionic acid collected. Yield, 85-90% of theory.

$\beta$ -4-Methoxyphenylpropionamide. Thionyl chloride (105 cc.) was added to a solution of  $\beta$ -4-methoxyphenylpropionic acid (125 g.) in chloroform (400 cc.), and the mixture was kept at room temperature for 24 hours. After being warmed gently for 1 hour, the liquid was cooled and poured into a mixture of concentrated ammonia solution (1750 cc.) and sodium hydroxide (71 g.). The chloroform and excess of ammonia were removed by distillation, the solution was cooled, and the solid thus obtained was recrystallised from a mixture of water (1750 cc.) and alcohol (250 cc.). Yield, 67% of theory.

$\beta$ -4-Methoxyphenylethylamine. The general method of Decker (Ann. 1913, 395, 291) was employed.  $\beta$ -4-Methoxyphenylpropionamide (50 g.) was added to a solution of sodium hypochlorite, prepared from 10% sodium hydroxide solution (550 cc.) and the calculated amount of chlorine (from hydrochloric acid and 16.5 g. potassium permanganate). The amide gradually dissolved, and the solution was heated to 70-80° for half an hour. Solid

potassium hydroxide (165 g.) was then added and the heating continued for three hours at the same temperature. The amine was extracted with benzene (400 cc.), the solvent was removed from the extract by distillation, and the amine purified by distillation under reduced pressure. Yield, 45% of theory, b.p. 145-165°/36 mm.; 127-130°/12 mm.

2'-Nitro-3':4'-dimethoxyphenylaceto- $\beta$ -4-methoxyphenylethylamide.

2-Nitro-3:4-dimethoxyphenylacetyl chloride (from 12 g. of the acid) dissolved in dry benzene (30 cc.) was added slowly to a solution of  $\beta$ -4-methoxyphenylethylamine (8 g.) in dry benzene (30 cc.). A buff-coloured precipitate was formed; excess of 10% sodium hydroxide solution was then added, and the amide which separated was collected. A further amount was obtained by separation and evaporation of the benzene. Yield, 97% of theory. Recrystallisation from 70% aqueous alcohol **yielded** 2'-nitro-3':4'-dimethoxyphenylaceto- $\beta$ -4-methoxyphenylethylamide as colourless needles, m.p. 97.5° (Found: C, 61.2; H, 5.9.  $C_{19}H_{22}O_6N$  requires C, 61.0; H, 5.9%). When crystallised from benzene, the amide formed needles, m.p. 76-88° containing one molecule of benzene of crystallisation (Found: Loss at 97°, 16.8. Calculated: 17.2%).



The Dehydration of the Amide. - The dehydration was first attempted under the conditions used in previous syntheses of this type.

In one experiment the amide, containing benzene of crystallisation, (4 g.) was added to a solution of phosphorus pentachloride (5 g.) in chloroform (30 cc.), and the mixture was preserved in a closed tube. No solid separated after four days. Half the solution was then withdrawn, and the solvent removed in a desiccator under reduced pressure. The residual gum was extracted with boiling water, and the extract made alkaline with ammonia. No precipitate was formed. The residue slowly solidified, and on recrystallisation from alcohol, the pure amide was recovered. The remaining half of the original reaction-mixture was kept out of contact with moisture, but no separation of solid had taken place after one month. In another experiment the amide (5 g.), dried at  $75^{\circ}$ , was added to a saturated solution of phosphorus pentachloride (12 g.) in chloroform (100 cc.) which had been freshly distilled over phosphoric oxide. After 48 hours the crystalline crust which had separated was removed, but this proved to be merely phosphorus pentachloride. The chloroform was removed from the solution by evaporation on a boiling water-bath under reduced pressure for  $1\frac{1}{2}$  hours, and the black, tarry residue was extracted with boiling water. On making the aqueous

extract alkaline, a slight buff precipitate was formed, but the amount was too small for examination. Treatment of the residual tar with alcohol yielded a small quantity of a crystalline substance (A), identified later with the product obtained in hot solvents in presence of phosphoric oxide and phosphorus pentachloride.

Further experiments included (a) a repetition of that described above, with the addition of phosphoric oxide at the end of 36 hours; (b), the action of phosphorus pentachloride and anhydrous aluminium chloride in cold and in warm benzene or chloroform: (c), the action of anhydrous ferric chloride alone and with phosphorus pentachloride: and (d), the action of phosphoric oxide in boiling benzene or chloroform. In no case could a basic product be isolated.

In an experiment in which the amide (0.5 g.) was heated for one hour in boiling chloroform (5 g.) with phosphoric oxide (0.2 g.) and phosphoryl chloride (0.8 g.) the chloroform solution yielded a crystalline substance (B) when evaporated. A similar crystalline substance (C) (0.5 g) was obtained by heating the amide (1.0 g.) in boiling benzene or toluene (10 g.) with phosphoric oxide and phosphorus pentachloride (0.5 g.) The substances (A), (B), and (C) were proved to be identical by taking mixed melting-points. Recrystallisation from benzene yielded microscopic brown needles of a non-basic compound, m.p.

142.5-144° (Found: C, 64.5; H, 5.9; N, 7.6%). Repeated recrystallisation from light petroleum yielded light yellow needles, m.p. 143.5-144° (Found by microanalysis: C, 64.3; H, 5.8; N, 7.7. Calc. for  $C_{19}H_{20}O_5N_2$ : C, 64.0; H, 5.6; N, 7.9%).

### Nitration of $\beta$ -4-Methoxyphenylethylamine.

Method I. Nitration in Fuming Nitric Acid. - Results which were promising at first sight were obtained by following the method used by Goss, Hanhart, and Ingold (J.C.S., 1927-250) for the nitration of  $\beta$ -phenylethylamine.  $\beta$ -4-Methoxyphenylethylamine (6 g.) was added very gradually to fuming nitric acid (d. 1.5; 30 cc.) which was stirred vigorously and cooled in ice and salt. Stirring was continued for 10 minutes after the addition of the amine, and the mixture was then poured onto ice. A yellowish-buff precipitate (6.0 g) was obtained which was collected, and when dried on porous plate melted at 148° (decomp.). This product appeared to be decomposed by water, with which it developed a red colour, but it crystallised well from 2N nitric acid. After two recrystallisations,  $\beta$ -3:5-dinitro-4-methoxyphenylethylamine nitrate was obtained as pale-yellow, microscopic plates, m.p. 155-155.5° (decomp.) (Found: C, 35.7; H, 4.1; N, 18.2.  $C_9H_{11}O_5N_3 \cdot HNO_3$  requires C, 35.5; H, 4.0; N, 18.4%).

Several attempts were made to separate the base from this nitrate. The action of warm, dilute sodium hydroxide solution yielded a reddish-yellow tar which soon solidified. The solid was only partly soluble in dilute nitric acid, concentrated hydrochloric acid, or boiling dilute sodium hydroxide solution. It was insoluble in methyl or ethyl alcohols. The sodium hydroxide extract slowly deposited small purple nodules of a substance which exploded on heating. A red precipitate was formed by the addition of alcohol to the alkaline mother-liquors. The treatment of both these products with dilute nitric acid yielded a green solid, which exploded spontaneously when preserved. The gradual addition of ammonia to a cooled solution of the nitrate yielded a red, gummy precipitate, which slowly solidified, and was removed by filtration. The filtrate deposited a yellow solid. Neither of these products was redissolved completely by dilute nitric acid. In other experiments, mixtures of dark nodules and a yellow flocculent solid or microscopic yellow needles [m.p. 155-165° (decomp.) in one case] were obtained. These were sparingly soluble in the usual solvents.

The addition of a slight excess of ammonia to the mother-liquors of the recrystallisation of  $\beta$ -3:5-dinitro-4-methoxyphenylethylamine nitrate yielded a bright-red,



crystalline precipitate which darkened slowly above  $220^{\circ}$  and did not melt below  $300^{\circ}$ . No suitable solvent having been found for recrystallisation, the substance was analysed without purification (Found: C, 41.4; H, 4.1; N, 17.5.  $C_8H_9O_5N_3$  requires C, 42.3; H, 4.0; N, 18.5). Treatment with a boiling N/5 alcoholic picric acid solution yielded a mixture of a red powder and yellow needles. The latter substance, which predominated, was purified by repeated recrystallisation from water. It then melted at  $209-209.5^{\circ}$  (decomp.), and appeared to be identical with  $\beta$ -3:5-dinitro-4-hydroxyphenyl-ethylamine picrate (Found: N, 18.3.  $C_8H_9O_5N_3$ ,  $C_6H_3O_7N_3$  requires N, 18.4%). (Waser and Sommer, *Helv. Chim. Acta*, 1923, 6, 54, give m.p.  $196^{\circ}$  for the picrate, and state that the base decomposes without melting at  $209^{\circ}$ ).

Method II. Nitration in Nitric Acid treated with Urea Nitrate.

$\beta$ -4-Methoxyphenylethylamine (7 g.) was added slowly to ice-cold nitric acid (30 cc.) prepared by warming concentrated nitric acid (d 1.4) with urea nitrate (1.5 g.) On pouring the mixture onto ice, a slight oily precipitate was formed. This was removed, and the filtrate made alkaline with ammonia and extracted with ether. The ether was extracted with dilute hydrochloric acid, and evaporation of the acid extract to dryness yielded a solid from which colourless crystals of



$\beta$ -4-methoxyphenylethylamine hydrochloride, m.p. 206-208°, were obtained by crystallisation from the minimal volume of methyl alcohol.

In a second experiment the amine (6 g.) was added to nitric acid (25 cc.) prepared by treating fuming nitric acid (d 1.5) with a large excess of urea nitrate.  $\beta$ -4-Methoxyphenylethylamine hydrochloride was again isolated in an amount roughly equivalent to the quantity of material used.

Method III. Nitration in Acetic Acid. -  $\beta$ -4-Methoxyphenylethylamine (6 g.) in glacial acetic acid (24 g.) was added to a mixture of glacial acetic acid (12 g.) and nitric acid (12 g.) which had been prepared by treating fuming nitric acid (d 1.5) with a large excess of urea nitrate. No perceptible action took place until the mixture was warmed for 40 minutes at 50-75°. No separation of solid took place on adding water, and the addition of ammonia yielded a brown solid (1.9 g.) which was recognised as  $\beta$ -3:5-dinitro-4-hydroxyphenylethylamine by conversion into the picrate, m.p. 209-209.5° (decomp.).

The nitration of  $\beta$ -4-methoxyphenylethylamine hydrochloride under similar conditions yielded very small quantities of solid black products.

Method IV. Nitration in Concentrated Sulphuric Acid.

$\beta$ -4-Methoxyphenylethylamine sulphate was obtained as colourless leaflets, m.p. above  $280^{\circ}$ , by dissolving the amine in the calculated quantity of hot 20% sulphuric acid, and cooling the solution. A mixture of nitric acid (d.1.4; 3.5 g) and concentrated sulphuric acid (12.5 cc.) was slowly added to a mechanically-stirred solution of the sulphate (7.5 g.) in concentrated sulphuric acid (12.5 cc.), which was cooled in a freezing mixture. The product was poured onto ice, and the yellow precipitate (9.2 g) was collected by filtration. This substance was readily soluble in dilute aqueous sodium hydroxide, and was reprecipitated by acid. It was insoluble in the usual organic solvents, but dissolved in 60 parts of boiling water, from which it separated on cooling as brown rectangular plates mixed with a few dark-brown needles. The plates and needles, either separately or mixed, blackened at  $293^{\circ}$  and melted at  $297^{\circ}$  with decomposition and effervescence. Either the plates or the needles, when recrystallised from dilute sulphuric acid, yielded  $\beta$ -3-nitro-4-methoxyphenylethylamine-5-sulphonic acid as a pale orange mixture of plates and needles which lost water at about  $140^{\circ}$ , becoming light-yellow, darkened at about  $290^{\circ}$ , and did not melt below  $310^{\circ}$  (Found in material dried at  $135^{\circ}$ :

C, 39.1; H, 4.5; S, 11.7. Calc. for  $C_9H_{12}O_6N_2S$  C, 39.1; H, 4.4; S, 11.6%). The plates and needles, which had been separated mechanically from a well-crystallised specimen, lost practically the same percentage weight on heating, corresponding to one mol. of water of crystallisation (Found, loss at  $145^\circ$ : Needles, 6.0% Plates, 5.9% Calc. for  $C_9H_{12}O_6N_2S \cdot H_2O$  6.1%).

One experiment was made to try to eliminate the sulphonyl group by means of superheated steam. Signs of decomposition were noticed at  $190-200^\circ$ , when the substance began to char and the condensate became slightly oily and evil-smelling.

Nitration of  $\beta$ -4-Methoxyphenylpropionic Acid. The nitration of  $\beta$ -4-methoxyphenylpropionic acid in nitric acid took place smoothly. The best yield of  $\beta$ -3-nitro-4-methoxyphenylpropionic acid was obtained by the following method. Dry, powdered  $\beta$ -4-methoxyphenylpropionic acid (66 g.) was added slowly to vigorously stirred nitric acid (390 cc., d 1.42), the temperature being allowed to rise from  $10^\circ$  to  $25^\circ$ . Stirring was continued for ten minutes after all the acid had dissolved, and the mixture was then slowly poured onto ice (600 g.). The nitration-product separated as a yellow oil which quickly solidified. It was collected and dried, and was then sufficiently pure for use in the next stage (yield,

56.5 g; m.p. 110-120°). The acid was purified for analysis by recrystallisation from dilute aqueous methyl alcohol, precipitation from benzene by light petroleum, recrystallisation from water, and finally by recrystallisation from carbon tetrachloride. The m.p. was unchanged by the last crystallisation, which yielded  $\beta$ -3-nitro-4-methoxyphenylpropionic acid as pale-yellow needles, m.p. 128-130.5° (Found: N, 6.0.  $C_{10}H_{11}O_5N$  requires N, 6.0%). The acid was very soluble in methyl alcohol, ethyl alcohol, chloroform, and benzene; moderately soluble in boiling, and slightly soluble in cold, water; slightly soluble in boiling, and practically insoluble in cold, carbon tetrachloride; and insoluble in light petroleum.

The filtrate from the crude  $\beta$ -3-nitro-4-methoxyphenylpropionic acid deposited a mixture (16 g) of a reddish-yellow oil and crystals. After repeated recrystallisation from dilute acetic acid and from 50% aqueous alcohol, fine, light-yellow, glistening plates, m.p. 133-138°, were obtained. Since repeated recrystallisation did not raise the melting point, the substance was purified by precipitation of the reddish-yellow barium salt from a dilute ammoniacal solution by addition of barium chloride, decomposition of this salt by dilute hydrochloric acid yielded the product which was recrystallised from boiling water. It then had m.p. 136-139°.



(Found: C, 42.5; H, 3.3; N, 11.3. Calc. for  $C_9H_8O_7N_2$ : C, 42.2; H, 3.1; N, 10.9%). This substance was evidently

$\beta$ -3:5-dinitro-4-methoxyphenylpropionic acid.

$\beta$ -3-Nitro-4-methoxyphenylpropionamide. The amide was obtained in moderate yield by the usual method. Thionyl chloride (70 g.) was added to the acid (53 g.) in chloroform (300 cc.), and the mixture was left to stand overnight. After being warmed for 3 hours at  $40^\circ$ , the solution was poured into concentrated ammonia (900 cc. d 0.88) containing sodium hydroxide (25 g.). When the chloroform was removed by distillation,

$\beta$ -3-nitro-4-methoxyphenylpropionamide separated from the hot solution (yield, 35.5 g; m.p.  $123-127^\circ$ ). The product was purified for analysis by recrystallisation from benzene and from water. It separated from the latter solvent in pale-yellow, hexagonal plates, m.p.  $126.5-127^\circ$  (Found: N. 12.2  $C_{10}H_{12}O_4N_2$  requires N, 12.5%).

The ammoniacal mother-liquors of the crude amide yielded a yellow precipitate when acidified with dilute sulphuric acid. Purification by recrystallisation proved unsatisfactory, and the substance was ultimately purified by repeated solution in dilute sodium hydroxide and reprecipitation by acid. It was thus obtained as a canary-yellow powder, m.p.  $126-128^\circ$  (Found: N, 6.6%. Calc. for  $C_9H_9O_5N$ , N, 6.6%). The substance



thus appeared to be  $\beta$ -3-nitro-4-hydroxyphenylpropionic acid.

$\beta$ -3-Nitro-4-methoxyphenylethylamine. The amine was prepared from the amide by the usual method.  $\beta$ -3-Nitro-methoxyphenylpropionamide (37.5 g.) was treated with a solution of sodium hypochlorite prepared from sodium hydroxide solution (400 cc. of 2N) and chlorine (from the calculated quantity of potassium permanganate; 15 g.). When the solution had been maintained at 70-80° for half an hour, solid potassium hydroxide (100 g.) was added, and the mixture kept at 70-80° for 2 hours. When cold, the mixture was extracted with benzene (12. in five portions), and the benzene was then extracted with dilute hydrochloric acid (300 cc. of 2N). The acid solution was evaporated to a paste on the water-bath, and the resulting hydrochloride (16 g) recrystallised from methyl alcohol (100 cc.) A final recrystallisation from absolute methyl alcohol (2.5 parts) yielded  $\beta$ -3-nitro-methoxyphenylethylamine hydrochloride as yellow needles, m.p. 231-232°. (Found: N, 11.9.  $C_{19}H_{12}O_3N_2$ , HCl requires N, 12.0%). The base was obtained as an oil when the aqueous solution of the hydrochloride was made alkaline with sodium hydroxide. Treatment with benzoyl chloride in presence of sodium hydroxide yielded the benzoyl derivative, which crystallised from alcohol or benzene in yellow needles; these became red

in the light; m.p. 129-130° (Found: C, 63.7; H, 5.1.

$C_{16}H_{16}O_4N_2$  requires C, 64.0; H, 5.3%).

$\beta$ -3-Amino-4-methoxyphenylethylamine.  $\beta$ -3-Nitro-4-methoxyphenylethylamine hydrochloride (15.7 g.) was dissolved in acetic acid (40 cc.) and concentrated hydrochloric acid (40 cc.), the solution raised to the boiling point, and stannous chloride (30 g., 6 mols.) added gradually. A bulky precipitate separated at first, but disappeared as the reduction proceeded. The cooled solution was made alkaline by the addition of a large excess of sodium hydroxide solution (100 g. in 400 cc.), and was extracted with ether.  $\beta$ -3-Amino-4-methoxyphenylethylamine dihydrochloride (9.4 g) was precipitated by passing hydrogen chloride into the dried ethereal solution, and melted at 248-251° (decomp.). It was purified for analysis by dissolving in warm 95% alcohol and adding ether to the warm solution until separation began. The dihydrochloride was thus obtained as white needles, m.p. 253-254° (decomp.) after darkening. (Found, by titration: Cl, 29.8. Calc. for  $C_{19}H_{14}ON_2 \cdot 2HCl$ : Cl, 29.7%)

2-Nitro-3:4-dimethoxyphenylacetylation of  $\beta$ -3-Amino-4-methoxyphenylethylamine.

$\beta$ -3-Amino-4-methoxyphenylethylamine dihydrochloride

(2.4 g.) was decomposed by means of aqueous sodium hydroxide, and the oily base extracted with benzene. The benzene extract was added to a cooled solution in benzene (40 cc.) of 2-nitro-3:4-dimethoxyphenylacetyl chloride (prepared from the acid 4.8 g., 2 mols.). After the addition of sodium hydroxide solution in slight excess and filtration to remove a small quantity of tar, the benzene layer was separated, and evaporated. The gummy residue crystallised when rubbed with a little methyl alcohol (yield, 5.7 g), when recrystallised from methyl alcohol, 2'-nitro-3':4'-dimethoxyphenylaceto- $\beta$ -3-(2"-nitro-3":4"-dimethoxyphenylacetamido)-4-methoxyphenylethylamide was obtained as white needles, m.p. 158-159° (Found: N, 9.0.  $C_{29}H_{32}O_{11}N_4$  requires N, 9.1%). This substance was moderately soluble in benzene, from which it separated slowly in ill-defined crystals.

An attempt was made to prepare 2'-nitro-3':4'-dimethoxyphenylaceto- $\beta$ -3-amino-4-methoxyphenylethylamide by adding the acid chloride (1 mol.) to the amine. When hydrogen chloride was passed into the dry benzene solution, a tarry precipitate was obtained. This was separated and stirred with dilute hydrochloric acid. A solid residue of the impure diacylamide remained, and the solution, on evaporation, yielded white crystals of the diamine dihydrochloride. The identity of each was confirmed by mixed melting points. Using 2.6 g.

diamine dihydrochloride, the weights of diacyl amide and diamine dihydrochloride isolated were, respectively, 1.6 g. and 0.2 g.

Treatment of the Amide with Phosphorus Pentachloride.

The first attempt to prepare the isoquinoline derivative from the amide was carried out in the usual way and with the usual precautions. Phosphorus pentachloride (3 g.) was dissolved in chloroform (20 g.) which had been freshly distilled from phosphoric oxide, and the amide (3 g.) was added. The solution quickly turned reddish-brown, but no separation of solid had occurred after keeping in a closed flask for six days. The fact that no considerable amount of any strongly basic compound had been formed was shown by boiling a portion of the reaction-mixture with water until all the chloroform had been removed, filtering, and making the filtrate alkaline with ammonia. Only a very slight flocculent precipitate was formed. The remainder of the reaction-mixture was treated with water and evaporated under reduced pressure at the ordinary temperature. The condensation-product (3.6 g.) thus obtained was a dark brittle gum, insoluble in acids, which was ground up to a yellow powder, m.p.  $87-100^{\circ}$  (decomp.).

A preliminary examination of this condensation-product suggested that it contained a feebly basic compound combined with phosphoric or hydrochloric acid. The supposed base



could be obtained as a tar by basifying the acid methyl-alcoholic solution with ammonia. An amorphous purple powder, m.p.  $87-95^{\circ}$  (decomp.), was obtained by redissolving the tar in methyl alcohol and precipitating by the addition of water, but no crystalline substance could be obtained in this way. Picric acid in ethyl alcohol yielded a dark-yellow, oily precipitate which did not become crystalline after two separations from methyl alcohol. The supposed base was also obtained in benzene solution when the condensation-product was stirred with benzene and concentrated ammonia. The benzene solution gave a red tar when evaporated, and attempts to prepare a hydrochloride by passing hydrogen chloride into the benzene solution, or a methiodide by boiling with methyl iodide yielded tarry products. When heated with concentrated hydrochloric acid under reflux, partial solution occurred, and after removal of tar, the addition of ammonia produced a small amorphous precipitate which appeared to consist of a primary amine, for a deep-red colour was obtained when the substance was diazotised in hydrochloric acid and added to an alkaline solution of  $\beta$ -naphthol.

On the basis of this preliminary examination, an attempt was made to separate a pure product as a picrate. The condensation was carried out as before, but the chloroform solution was exhaustively washed with water. The washings became slightly



cloudy when basified with ammonia. The chloroform solution yielded a red, brittle gum on evaporation to dryness under reduced pressure at the ordinary temperature. A tarry picrate was prepared in absolute alcoholic solution, and after recrystallisation from absolute ethyl alcohol, and fractional precipitation from benzene by light petroleum, a light-yellow, microcrystalline solid was obtained, softening at  $92^{\circ}$ , melting at  $105-115^{\circ}$ , decomposing at  $120^{\circ}$ . Treatment with dilute sodium hydroxide yielded a yellow powder, m.p.  $103-120^{\circ}$  (decomp.) after softening at  $93^{\circ}$ . An attempt to crystallise this from alcohol yielded only a trace of amorphous material, and the investigation by this method was abandoned, since the quantity of available material was rapidly diminishing.

Further endeavours to elucidate the nature of the condensation-product were confined to an examination of the product of its hydrolysis with concentrated hydrochloric acid. Hydrolysis was carried out by heating the condensation-product under reflux on the water-bath with concentrated hydrochloric acid (10 parts) for two hours. The dark solution was separated from the tar by filtration, and made alkaline with ammonia. A yellow precipitate, m.p.  $68-88^{\circ}$  or  $65-75^{\circ}$  in different experiments, was obtained in a yield of 19-20% by weight. It was very soluble in alcohol, sparingly soluble in benzene or light petroleum, and attempts to crystallise it were unsuccessful. The addition of an excess of an alcoholic solution of

of picric acid to the alcoholic solution of the base, followed by the addition of water, yielded a precipitate which was repeatedly recrystallised from dilute alcohol. The picrate thus obtained formed yellow-brown needles, m.p. 194-198° (decomp.) (Found: C, 49.7; H, 4.2.  $C_{19}H_{21}O_5N_3$ ,  $C_6H_3O_7N_3$  requires C, 50.0; H, 4.0%). Treatment of the picrate with cold 2N sodium hydroxide solution yielded the base as a brown powder, which was purified by repeated crystallisation from light petroleum (b.p. 100-120°), from which it separated as microscopic yellow needles, m.p. 169.5-170° (Found, by microanalysis: C, 61.1; H, 5.8; N, 11.2.  $C_{19}H_{21}O_5N_3$  requires C, 61.4; H, 5.7; N, 11.3%). The base became gummy and then slowly dissolved when treated with dilute hydrochloric acid. When this solution was treated with sodium nitrite and added to an alkaline solution of  $\beta$ -naphthol, a deep, cherry-red colour was developed. Treatment with benzoyl chloride and sodium hydroxide yielded a benzoyl derivative, which formed microscopic yellow crystals, m.p. 188-195°, when crystallised from dilute methyl alcohol or light petroleum. It was insoluble in dilute hydrochloric or sulphuric acid.

In 1913, Ray and Pictet (2, 1913, 105, 985) endeavored to synthesize apomorphine dimethylether (II) by submitting 2-nitro-3,4-dimethoxyphenylacetic acid (I) to the action of phosphorus pentoxide. They did not succeed in obtaining their object, however, since the only substance which they were able to isolate was a substance, isomeric with the desired product, to

### PUBLICATION 20.

which they assigned the name "apomorphine" twelve years later, Gossauer, Gossauer, and Gossauer (3, 1925, 985, 986) attempted syntheses of apomorphine dimethylether.

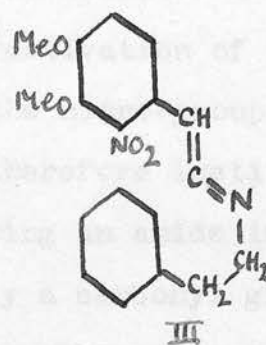
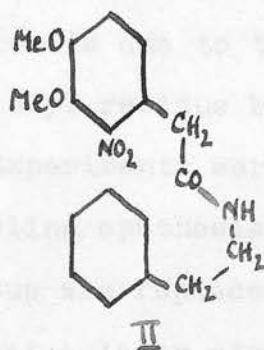
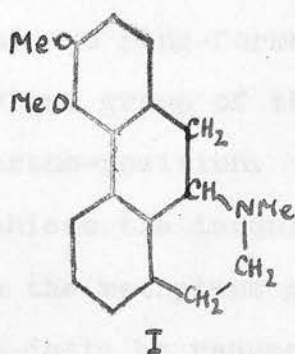
### ATTEMPTED SYNTHESSES OF APOMORPHINE DIMETHYLETHER.

2-nitrophenylacetic acid (I) was converted to 2-nitrophenylacetic acid (I) by a similar course.

Part of the work described in this paper was carried out personally by the author. The remainder of the experiments were performed either by Mr. C. J. Virden or by Mr. R. K. Callow with the daily guidance and help of the author, and under his supervision.

For the synthesis of apomorphine dimethylether, or of similarly substituted substances which cannot be obtained by the Fischer-Karlberg reaction, and as mentioned above, it was essential to repeat some of the experiments described above. The results of Ray and Pictet were therefore reinvestigated, and their results have been confirmed and

In 1913, Kay and Pictet (J.1913.103.950) endeavoured to synthesise apomorphine dimethylether (I) by submitting 2-nitro-3:4-dimethoxyphenylaceto- $\beta$ -phenylethylamide (II) to the action of phosphoric oxide. They did not succeed in attaining their object, however, since the only substance which they were able to isolate was a non-basic compound, isomeric with the expected isoquinoline derivative, to which they assigned the constitution (III). Twelve years later, Gadamer, Oberlin, and Schoeler (Arch. Pharm. 1925. 263.81) observed that the action of phosphoric oxide on 2-nitrophenylaceto- $\beta$ -phenylethylamide followed a similar course.



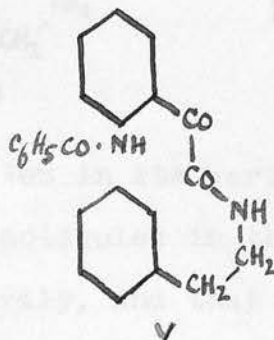
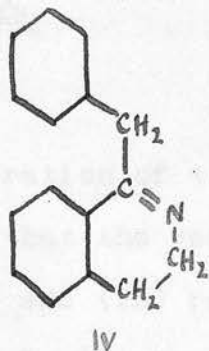
Before proceeding to the examination of other methods for the synthesis of apomorphine or its dimethylether, or of similarly constituted alkaloids which cannot be obtained by the Bischler-Napieralski reaction, such as isothebaine, it was essential to repeat some of the experiments described above. The researches of Kay and Pictet were therefore reinvestigated, and their results have been confirmed and

extended. This work may be summarised by stating that dehydrating agents, for example phosphorus pentachloride and phosphoric oxide, either have no effect on the amide (II), or else convert it into the non-basic substance (III). Elevated temperatures favour the occurrence of the second type of reaction.

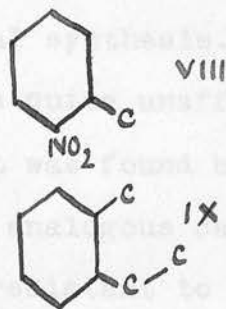
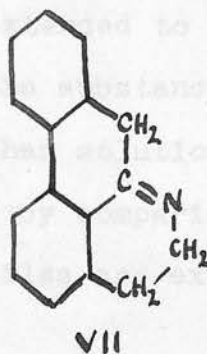
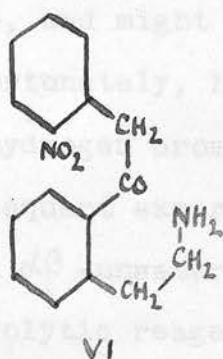
Now, the Bischler-Napieralski reaction may be successfully employed for the conversion of phenylaceto- $\beta$ -phenylethylamide into benzyldihydroisoquinoline (IV) (Pictet and Kay, Ber.1909.42.1973; Decker and Kropp, *ibid.*2075; Decker, Kropp, Hoyer, and Becker, Ann.1913.395.299), and thus it is evident that the failure of the nitrated amides to undergo ring-formation is due to the activation of the methylene group of the acyl residue by the nitro-group in the ortho-position. Experiments were therefore instituted to achieve the isoquinoline synthesis using an amide in which the methylene group was replaced by a carbonyl group, which could be reduced at a later stage. The preparation of 2-nitro-3:4-dimethoxyphenylglyoxylic acid for this purpose by the interaction of 2-nitro-3:4-dimethoxybenzoyl chloride and silver cyanide proved most unsatisfactory, and attention was therefore directed to the use of benzoylamino-phenylglyoxylic acid, which may be obtained from isatin by benzoylation in alkaline solution (Schotten, Ber.1891.24.773). When some preliminary difficulties in the preparation of the acid chloride had been surmounted



benzoylamino-phenylglyoxylo- $\beta$ -phenylethylamide (V) was submitted to the action of dehydrating agents. Unfortunately no isoquinoline derivative could be isolated, and this method of attacking the problem was therefore abandoned.



The ease with which a carbonyl- and an amino-group lose the elements of water to form a five- or a six-membered ring has for long seemed to the author to offer a possible means of building-up the nitrogenous ring of the aporphines onto a preformed phenanthrene system. If this were possible, the difficulties presented by the synthesis of apomorphine and isothebaine would be overcome. The experiments carried out with this object in view have not so far been successful, but they reveal several points of interest. The fundamental idea has been the preparation of a substituted desoxybenzoin (VI) or an allied substance, which would not only undergo the Pschorr reaction forming a phenanthrene derivative, but would also lose with ease the elements of water, yielding a dihydroisoquinoline (VII).

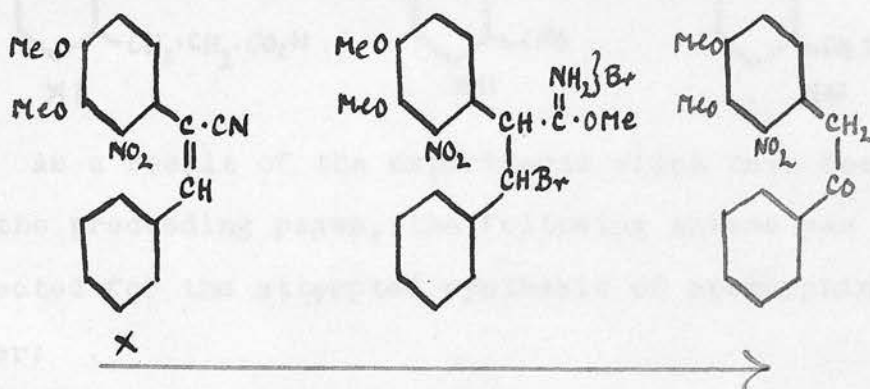


A consideration of the problem in its various aspects made it clear that the reacting molecules in the synthesis must be (VIII) and (IX) respectively, and that processes such as the Friedel-Crafts reaction could not be employed. In furtherance of this idea, it seemed that 2-nitro-3:4-dimethoxybenzyl cyanide was the most suitable compound containing activated hydrogen atoms on the  $\alpha$ -carbon atom, and a number of preliminary experiments were performed under varied conditions in order to test the possibility of preparing a desoxybenzoin derivative by the action of ethyl benzoate or benzoyl chloride on the sodio-derivative of this nitrile. No crystalline product could be isolated; this result may be due to the interaction of two molecules of the nitrile in the manner observed in the case of benzyl cyanide by Atkinson and Thorpe (J.1906.89.1913) and by Lees and Thorpe (J.1907.91.1287).

2-Nitro-3:4-dimethoxybenzyl cyanide and benzaldehyde readily reacted in sodium ethoxide solution yielding

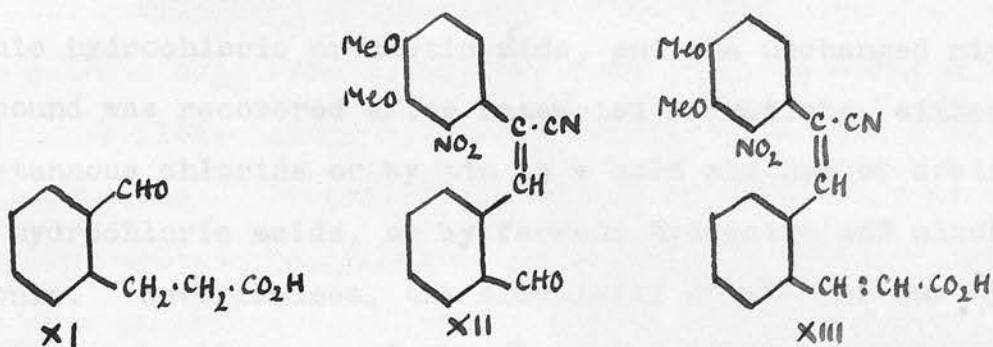
$\alpha$ -cyano-2-nitro-3:4-dimethoxystilbene (X), and it was

hoped that the following series of changes might be practicable, and might then be extended to the actual synthesis. Unfortunately, however, the substance (X) was quite unaffected by hydrogen bromide in ether solution, and it was found by subsequent experiment and by comparison with analogous cases that  $\alpha\beta$ -unsaturated nitriles are extremely resistant to hydrolytic reagents.

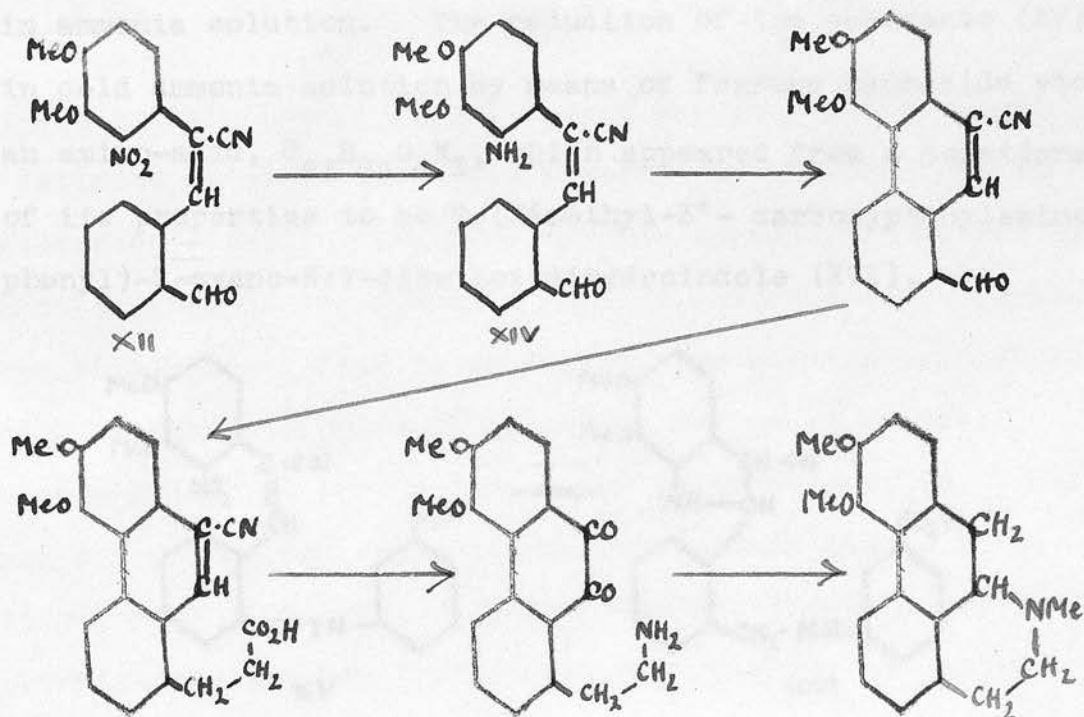


Efforts to employ a derivative of desoxybenzoin were then abandoned, and it was decided to take advantage of the ease with which 2-nitro-3:4-dimethoxybenzyl cyanide condenses with aldehydes. The requisite  $\beta$ -o-aldehydophenylpropionic acid (XI) was unknown, and fruitless attempts were made to prepare it either by the condensation of phthalaldehyde with malonic acid, or by the reduction of the cyano-group of  $\beta$ -o-cyanophenylpropionic acid (Edwards, J.1926,813) by the method of Stephen (J.1925.127.1874). Conditions were then devised for the preparation of  $\alpha$ -cyano-2-nitro-3:4-dimethoxy-2'-aldehydstilbene (XII) by the condensation of phthalaldehyde with 2-nitro-3:4-dimethoxybenzyl cyanide, but this

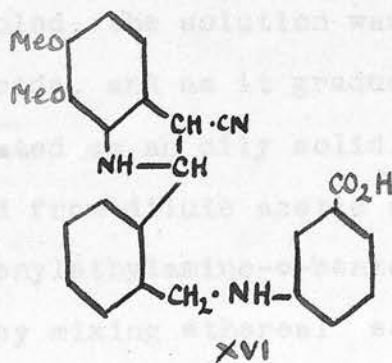
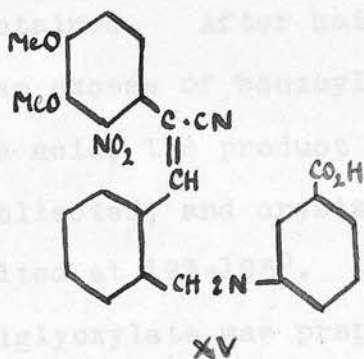
aldehyde (XII) yielded no crystalline material when heated with malonic acid and piperidine in pyridine solution with the object of obtaining the unsaturated acid (XIII).



As a result of the experiments which have been described in the preceding pages, the following scheme was ultimately selected for the attempted synthesis of apomorphine dimethylether:



The preparation of the substance (XIV) by the reduction of  $\alpha$ -cyano-2-nitro-3:4-dimethoxy-2'-aldehydstilbene offered considerable difficulty; no homogeneous material was obtained from the reduction by means of zinc and hot dilute hydrochloric or acetic acids, and the unchanged nitro-compound was recovered after attempted reductions, either by stannous chloride or by tin in a cold mixture of acetic and hydrochloric acids, or by ferrous hydroxide and alcoholic ammonia. Nevertheless, the simplicity of the ferrous hydroxide reductions in the case of the  $\alpha$ -aryl-2-aminocinnamic acids made this method worthy of further investigation, and the aldehyde (XII) was therefore converted into the Schiff's base,  $\alpha$ -cyano-2-nitro-3:4-dimethoxy-2'-aldehydaminophenyl-3"-carboxystilbene (XV) in order to render the material soluble in ammonia solution. The reduction of the substance (XV) in cold ammonia solution by means of ferrous hydroxide yielded an amino-acid,  $C_{25}H_{23}O_4N_3$ , which appeared from a consideration of its properties to be 2-(2-methyl-3"-carboxyphenylamino phenyl)-3-cyano-6:7-dimethoxydihydroindole (XVI).





This substance was soluble in alkali and in acid, and the prolonged action of boiling concentrated hydrochloric acid yielded only the corresponding hydrochloride, thus proving that the double-bond of the Schiff's base had been reduced. With nitrous acid, the sulphate formed a nitroso-compound which gave Liebermann's reaction, but diazotisation did not take place. Decomposition of the hydrochloride by means of sodium acetate regenerated the amino-acid (XVI) in the form of a polyhydrate, which was partly dehydrated when heated, and which was converted into the anhydrous compound by crystallisation from glacial acetic acid. Further details are described in the experimental section of this paper.

#### EXPERIMENTAL.

o-Benzoylaminophenylglyoxylic acid was prepared from sodium isatinate by benzoylating in presence of the least possible excess of alkali. Isatin (15g) was warmed with sodium hydroxide (100cc. of 2N; 2 mols.) until a clear yellow solution was obtained. After being cooled, the solution was shaken with an excess of benzoyl chloride, and as it gradually became acid, the product separated as an oily solid. This was collected, and crystallised from dilute acetic acid, when it melted at 193-195°.  $\beta$ -Phenylethylamine-o-benzoylamino-phenylglyoxylate was prepared by mixing ethereal solutions

of the amine and the acid. The caseous precipitate thus formed was crystallised from water, from which the salt separated in colourless needles, m.p. 177-179° (decomp.)

(Found: N, 7.4.  $C_{23}H_{22}O_4N_2$  requires N, 7.2%).

o-Benzoylaminophenylglyoxylo- $\beta$ -phenylethylamide. Fruitless attempts were made to prepare this amide from the salt described above by treating an ether suspension with phosphorus pentachloride or phosphoric oxide. Hydrolysis of the amide took place in every case. Efforts were then made to prepare o-benzoylaminophenylglyoxyl chloride by the interaction of the acid with thionyl chloride. An immediate reaction occurred when the acid and thionyl chloride were mixed, but the very unstable product decomposed so readily that other conditions were investigated. Finally, the amide was prepared by shaking the dry, powdered acid (2.5g) with thionyl chloride (20g). The acid dissolved, and the excess of thionyl chloride and the sulphur dioxide and hydrogen chloride were removed by repeated evaporation of the mixture with dry benzene. The residual benzene solution was then added gradually to a cooled solution of  $\beta$ -phenylethylamine (3g.; 2 mols.) in benzene. The resulting solution of the amide was washed with sodium carbonate, hydrochloric acid, and water, dried, and distilled. The residue was crystallised twice from alcohol, and the amide obtained as pale yellow needles, m.p. 136.5-138° (Found: C, 74.6; H, 5.5

$C_{23}H_{20}O_3N_2$  requires C, 74.2; H, 5.4%). The amide was recovered unchanged after being submitted to the action of phosphorus pentachloride in chloroform for one month, and was destroyed by treatment with phosphoric oxide in boiling toluene.

$\alpha$ -Cyano-2-nitro-3:4-dimethoxystilbene. A normal solution of sodium ethoxide in absolute alcohol was added gradually to a solution of 2-nitro-3:4-dimethoxybenzyl cyanide (1g) and benzaldehyde (0.5g) in a small quantity of warm absolute alcohol until a permanent reddish brown colouration was produced, and the mixture was maintained at  $55^\circ$  for one hour, and cooled. When the vessel was rubbed with a glass rod, the product separated, and was collected next day (yield, 0.78g). Several crystallisations from alcohol yielded a very pure specimen, m.p.  $125.5^\circ$ , which was readily soluble in ether and acetone (Found: C, 65.6; H, 4.5.  $C_{12}H_{14}O_4N_2$  requires C, 65.8; H, 4.6%). Piperidine may be used as a catalyst in place of sodium ethoxide, and the yield is unchanged. This substance was recovered unchanged from an ethereal <sup>methyl alcoholic</sup> solution which had been saturated with hydrogen bromide and preserved for some days.

$\alpha$ -Cyano-2-nitro-3:4-dimethoxy-2'-aldehydstilbene. Normal Sodium ethoxide solution (10.5cc.) was added to

2-nitro-3:4-dimethoxybenzyl cyanide (10g) and o-phthalaldehyde (5.6g) dissolved in a small quantity of warm absolute alcohol. The vigour of the reaction which soon began was checked by cooling the flask in running water, and the product separated as an oil which rapidly solidified. When recrystallised from alcohol, it formed long, colourless needles, m.p.  $153^{\circ}$ , which were sparingly soluble in the usual solvents (Found: C, 63.8; H, 4.3.  $C_{18}H_{14}O_5N_2$  requires C, 63.9; H, 4.1%). This substance was recovered unchanged from a suspension in concentrated hydrochloric acid which had been boiled for 24 hours. It was destroyed by the action of zinc dust in hot dilute acetic or hydrochloric acid, but was not reduced by treatment with stannous chloride or tin in a mixture of cold hydrochloric acid and acetic acid, nor by the action of ferrous hydroxide in alcoholic aqueous ammonia. The yield in the condensation was 80% of that theoretically possible; the use of piperidine as a catalyst depressed the yield and retarded the rate of the reaction.

A dark green amorphous precipitate was obtained by pouring into hydrochloric acid a mixture of the aldehyde (0.5g), malonic acid (0.75g), and piperidine (3 drops) which had been heated in pyridine at  $100^{\circ}$  for 2 hours. This precipitate was collected, extracted with sodium carbonate, and the extract was acidified with hydrochloric acid. The resulting pale brown amorphous solid was readily soluble in alcohol, acetone, acetic acid, and chloroform, sparingly



soluble in benzene, and insoluble in water and ligroin. No crystalline material was obtained from it. The phenylhydrazone separated from a solution of the aldehyde and phenyl hydrazine in warm glacial acetic acid, and was crystallised from alcohol in golden-yellow leaflets m.p. 179-180° (Found: N, 13.1.  $C_{24}H_{20}O_4N_4$  requires N, 13.1%).

Piperonylidene-m-aminobenzoic acid. This and the following experiment were carried out in order to investigate the conditions required for the preparation of Schiff's bases of this type.

An intimate mixture of piperonal and m-aminobenzoic acid was heated at 160° for 30 minutes, and the residue was crystallised from alcohol. It formed cream-coloured needles, m.p. 244-245°, which were very sparingly soluble in cold alcohol, and were rapidly hydrolysed by warm dilute mineral acids. (Found: C, 66.8; H, 4.2.  $C_{15}H_{11}O_4N$  requires C, 66.9; H, 4.1%). This substance was not reduced by treatment with ferrous hydroxide in cold ammoniacal solution in absence of air.

Piperonylidene-p-aminobenzoic acid, which did not crystallise well, was prepared in a similar manner. It formed brown nodules consisting of needles, m.p. 243° when crystallised from alcohol (Found: N, 5.3;  $C_{15}H_{11}O_4N$  requires N, 5.3%).



2-Cyano-2-nitro-3:4-dimethoxy-2'-aldehydaminophenyl-3"-carboxystilbene. An intimate mixture of m-aminobenzoic acid and 2-cyano-2-nitro-3:4-dimethoxy-2'-aldehydostilbene in equimolecular proportions was heated slowly in an oil bath. At 135°, the mass shrank together and became darker in colour, and the temperature was maintained at this point for 30 minutes. The residue was crystallised from alcohol, from which it separated in needles, m.p. 246° (decomp.) (Found: N, 9.2.  $C_{25}H_{19}O_6N_3$  requires N, 9.2%). This Schiff's base was readily hydrolysed by warm dilute mineral acids, and dissolved in dilute ammonia, from which it was precipitated in an amorphous condition by acetic acid. An ammoniacal solution decomposed when heated at 100° for a short time, changing in colour from bright yellow to green, and finally to black. An uncrystallisable material was obtained by acidification of this solution.

2-(2'-Methyl-3"-carboxyphenylaminophenyl)-3-cyano-6:7-dimethoxydihydroindole. This reduction had to be carried out at room temperature, since the ammoniacal solution of the Schiff's base was decomposed by heat.

A solution of the Schiff's base (0.8g) in air-free, ice-cold, dilute ammonia (20 cc.) was added to a solution of ferrous sulphate (4.4g) in ice-cold, air-free water (20cc.),

which was stirred mechanically in a flask fitted with a mercury-sealed stirrer and swept out by a stream of hydrogen. The initial green precipitate slowly darkened, and ultimately became quite black. The stirring was continued for 6 hours, and the mixture was then allowed to stand in the atmosphere of hydrogen until next day. The precipitated ferroso-ferric oxide was too finely divided to be collected on a filter, and charcoal was therefore added, and the solution acidified with dilute acetic acid. The solid was then collected at the pump, washed with water, and extracted with acetone in a Soxhlet apparatus for several hours. After the acetone had been removed by distillation, the crystalline residue was recrystallised from alcohol, and formed colourless needles, m.p.  $225^{\circ}$  (Found: C, 69.4; H, 5.0. By microanalysis, C, 70.0; H, 5.0; N, 9.8.  $C_{25}H_{23}O_4N_3$  requires C, 69.9; H, 5.3; N, 9.8%). This substance dissolved slowly in cold sodium hydroxide, sodium carbonate, or ammonia. It did not give the colour reactions characteristic of an indole. A solution in concentrated sulphuric acid developed a deep violet colour on the addition of sodium nitrite, and dilution and extraction with ether yielded a nitroso-compound (not isolated) which gave Liebermann's nitroso-reaction.

When the product of the reduction was heated with boiling dilute hydrochloric acid for a short time, it was

converted into the sparingly soluble, yellow hydrochloride, m.p.  $307^{\circ}$  (decomp.), which was analysed without further purification (Found: C, 62.7; H, 4.9; Cl, 7.2.  $C_{25}H_{23}O_4N_3 \cdot HCl \cdot H_2O$  requires C, 62.2; H, 5.4; Cl, 7.6%). This salt was sparingly soluble in cold water, but dissolved on boiling. If this solution, which was yellow and faintly cloudy, was allowed to cool without the vessel being scratched, the liquid set to a gel. If, on the other hand, the vessel was scratched, a solid separated which was faintly yellow in colour and melted over a wide range of temperature from  $200^{\circ}$  upwards. This was probably a mixture of the hydrochloride and the base, formed by hydrolysis. The hydrochloride was not altered by prolonged heating with concentrated hydrochloric acid.

When the hydrochloride was warmed gently with aqueous sodium acetate solution, a colourless crystalline substance, m.p.  $320^{\circ}$ , was deposited. It was sparingly soluble in the usual solvents, and was crystallised by dissolving it in much hot alcohol, filtering the solution, and concentrating the filtrate; it formed colourless needles, m.p.  $322^{\circ}$  (Found in different specimens: By macroanalysis, C, 67.2; H, 5.4; N, 9.2. By microanalysis, C, 60.2; H, 5.6; N, 8.5.  $C_{25}H_{23}O_4N_3 \cdot H_2O$  requires C, 67.2; H, 5.6; N, 9.4, and  $C_{25}H_{23}O_4N_3 \cdot 4H_2O$  requires C, 60.0; H, 6.2; N, 8.4%). It seemed probable that the two specimens were a tri- and a hexa-hydrate

respectively, since the first specimen when dried for analysis at  $100^{\circ}$  in an air oven lost 7.9% of its weight, and was then a monohydrate (Loss of  $2\text{H}_2\text{O}$  from  $\text{C}_{25}\text{H}_{23}\text{O}_4\text{N}_3 \cdot 3\text{H}_2\text{O}$  requires 7.7%), and the second specimen lost 6.9% of its weight when dried for analysis at  $110^{\circ}$  under reduced pressure in presence of phosphoric oxide (Loss of  $2\text{H}_2\text{O}$  from  $\text{C}_{25}\text{H}_{23}\text{O}_4\text{N}_2 \cdot 6\text{H}_2\text{O}$  requires 6.7%). This substance was an amino-acid, since it dissolved in sodium hydroxide, sodium carbonate, and ammonia, and regenerated the hydrochloride when treated with dilute hydrochloric acid. It could not be diazotised, and was converted into the reduction -product, m.p.  $225^{\circ}$ , when crystallised from glacial acetic acid.